A STUDY OF AUTONOMIC MODULATIONS WITH SHORT TERM HEART RATE VARIABILITY IN BRONCHIAL ASTHMA PATIENTS AND ITS CORRELATION WITH PULMONARY FUNCTION TESTS

Dissertation submitted for

M.D. (Branch – V Physiology)

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

Department of Physiology

PSG Institute of Medical Sciences and Research

Coimbatore – 641004

April 2015

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PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : psgethics2005@yahoo.co.in

March 21, 2013

To
Dr T Pushparaj
Postgraduate
Department of Physiology
PSG IMS & R
Coimbatore

Ref.: Proposal titled: *'A study of autonomic modulations with short term heart rate variability in bronchial asthma patients and to correlate it with pulmonary function tests'*

Sub.: Ethics Committee Approval for the study

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 27th February, 2013 in its full board review meeting held at College Council Room, PSG IMS&R, between 2.00 pm and 4.30 pm, and discussed your application to conduct the study entitled:

"A study of autonomic modulations with short term heart rate variability in bronchial asthma patients and to correlate it with pulmonary function tests'

The following documents were received for review:

1. Duly filled application form
2. Proposal
3. Informed Consent forms in English and Tamil
4. Data Collection Tool
5. CV
6. Budget

The members who attended the meeting at which your study proposal was discussed are as follows:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
2	Mrs. R. Geetha	+ 2	Lay person	Female	No	Yes
3	Mr Gowpathy Velappan	BA., BL	Legal Advisor	Male	No	Yes
4	Mrs G Malarvizhi	M Sc	Nursing	Female	Yes	Yes
5	Mr. R. Nandakumar (Vice-Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
6	Dr. G. Rajendiran	DM	Clinician (Cardiology)	Male	Yes	Yes
7	Dr. V. Ramamurthy	Ph D	Biotechnology	Male	Yes	Yes

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

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8	Dr. M. Ramanathan	M Pharm, Ph D	Non-Medical (Pharmacy)	Male	Yes	Yes
9	Dr. P. Sathyan (Chairperson, IHEC)	DO, DNB	Clinician (Opthalmology)	Male	No	No
10	Dr. Seetha Panicker	MD	Clinician (Obstetrics & Gyanaecology)	Female	Yes	No
11	Dr. S. Shanthakumari	MD	Pathology, Ethicist	Female	Yes	No
12	Dr. Y.S. Sivan	Ph D	Social Scientist (Sociology)	Male	Yes	Yes
13	Dr. Sudha Ramalingam (Alternate Member-Secretary, IHEC)	MD	Public Health, Epidemiology, Genetics, Ethicist	Female	Yes	Yes
14	Mrs. K. Uma Maheswari	M Sc, M Phil. B Ed	Botany	Female	No	Yes
15	Dr. D. Vijaya	M Sc, Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	No

After due consideration, the committee has decided to approve the above proposal.

The approval is valid for one year.

We request you to intimate the date of initiation of the study to IHEC, PSG IMS&R and also, after completion of the project, please submit completion report to IHEC.

We hereby confirm that neither you nor any of your study team members have participated in the voting/ decision making procedure of the committee. The members of the committee who have participated in the voting/ decision making procedure of the committee do not have any conflict of interest in the referenced study.

This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

PIs are required to send progress reports (in the form of an extended abstract with publications if any) to the IHEC every six months (and a month before expiry of approval date, if renewal of approval is being sought).

Request for renewal must be made at least a month ahead of the expiry of validity along with a copy of the progress report.

21.2.13

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee

SECRETARY PSG IMS & R COIMBATORE-641 004 INSTITUTIONAL HUMAN ETHICS COMMITTEE

Proposal No. 12/178

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

Recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
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March 7, 2014

To
Dr T Pushparaj
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PSG IMS & R
Coimbatore

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 7th March, 2014 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 10.00 am and 11.00 am, and discussed your application to renew the study entitled:

"A study of autonomic modulations with short term heart rate variability in bronchial asthma patients and to correlate it with pulmonary function tests"

The following documents were received for review:

1. Application for renewal
2. Status report of the study

After due consideration, the Committee has decided to renew the approval for the above study.

The members who attended the meeting held on at which your proposal was discussed, are listed below:

Name	Qualification	Responsibility in IHEC	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
Dr P Sathyan	DO, DNB	Clinician, Chairperson	Male	No	Yes
Dr S Bhuvaneshwari	M.D	Clinical Pharmacologist Member - Secretary	Female	Yes	Yes
Dr Sudha Ramalingam	M.D	Epidemiologist Alt. Member - Secretary	Female	Yes	Yes
Dr Y S Sivan	Ph D	Member –Social Scientist	Male	Yes	Yes
Dr D Vijaya	Ph D	Member – Basic Scientist	Female	Yes	Yes

The renewal is valid for one year (From 21.03.2014 to 20.03.2015).

This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Yours truly,

S. 3.17

Dr S Bhuvaneshwari
Member – Secretary

Proposal No. 12/178

PSG INSTITUTE OF MEDICAL SCIENCE & RESEARCH

PEELAMEDU, COIMBATORE – 4.

CERTIFICATE

This is to certify that the dissertation work entitled "A study of autonomic modulations with short term heart rate variability in bronchial asthma patients and its correlation with pulmonary function tests" submitted by Dr.T.Pushparaj, is the work done by him during the period of study of his post graduation in Physiology from June 2012 to March 2015 in our institution. This work is done under the guidance of Dr.T.Umamaheswari, Professor, Department of Physiology, PSG IMS &R.

Dr.T.Umamaheswari
Guide and Professor
Department of Physiology
PSG IMS & R.

Dr.M.Nagashree
Professor & Head
Department of Physiology
PSG IMS & R.

Dr.S.Ramalingam
Principal
PSG IMS & R.

DECLARATION

I hereby declare that this dissertation entitled “A study of autonomic modulations with short term heart rate variability in bronchial asthma patients and its correlation with pulmonary function tests” was prepared by me under the guidance and supervision of Dr.T.Umamaheswari, Professor, Department of Physiology, PSG IMS&R.

This dissertation is submitted to Tamilnadu Dr. MGR Medical University in fulfillment of the university regulations for the award of MD Degree in Physiology.

T.PUSHPARAJ

ACKNOWLEDGEMENT

First of all, I express my thanks to Dr.S.Ramalingam, Principal, PSG Institute of Medical Sciences and Research, for allowing me to do my dissertation in PSG IMS&R.

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I am also extremely grateful to Dr.RMPL.Ramanathan MD., Professor, Department of Pulmonology and Dr.R.Karthikeyan MD., Associate Professor, Department of Respiratory Medicine, PSG IMS&R, for providing patients for the study.

I also express my thanks to Dr.G.V.LathaDevi, Professor, Dr.P.Sathyavathi, Dr.V.Kannan, Dr.N.Shuba, Associate Professors and Dr. Deepalakshmi Assistant Professor, Department of Physiology, PSGIMS&R for helping me during the study.

I also want to express my sincere thanks to all other colleagues of my department as well as other department friends in PSGIMSR for their support and help that made this endeavor possible.

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Lastly, I pray and thank the Almighty and express my thanks to all the patients and volunteers involved in the study without which this study would have been impossible.

CONTENTS

ABSTRACT

TITLE

A study of autonomic modulations with short term heart rate variability in bronchial asthma patients and its correlation with pulmonary function tests

BACKGROUND

Asthma is a chronic inflammatory disease characterized by airway hyper-responsiveness, chronic wheezing, cough and chest tightness. Bronchial asthma is associated with positive family history hence the genetic history is predisposing factor in development of asthma. The previous studies showed that there was an imbalance favoring the parasympathetic system in the asthmatic airways. This study was done to compare the autonomic modulation between asthmatic patients and normal subjects based on short term heart rate variability.

METHODS

This cross sectional study involved 30 asthmatic patients and 30 normal subjects in an age group of 20 to 45 years. Spiropalm digital airflow spirometry was used to assess the pulmonary functions. Neviqure digital electrocardiography recorder was used to study 5 minutes HRV and Finland software was used for analysis of HRV. Data was analyzed by SPSS software using independent student t test, Chi square test and Pearson correlation analysis.

RESULTS

The time domains measures SDNN, RMSSD, NN50, and pNN50% are significantly decreased in asthmatics compared to the normal subjects. The frequency domain measures VLF and LF are decreased while HF is increased significantly in asthmatic patients. The Chi square test between bronchial asthma and positive family history shows that the person with positive family history of bronchial asthma has 45 times more chance of getting the disease. The Pearson correlation analysis shows HF has significant negative correlation with FEV_1%.

CONCLUSION

There is a significant increase in central vagal outflow and concomitant low sympathetic outflow in asthmatic patients. There is in an increased parasympathetic activity with increase in the severity of bronchial asthma. Low beat to beat variability is observed in asthmatics which is a predictor of cardiac mortality and morbidity. 90% of bronchial patients have positive family history.

KEYWORDS

Heart Rate Variability, Bronchial Asthma, Pulmonary Function Tests.

INTRODUCTION

HISTORY OF ASTHMA:

Asthma is derived from the Greek word ***aazein*** means "panting" and it was first described by Homer. Hippocrates medically defined asthma as "anything that causes shortness of breath"[1].

In 1678, Thomas Willis described asthma as "obstruction of bronchi by thick humors, swelling of their walls and obstruction from without"[2]. Roman doctors described asthma as "gasping and the inability to breathe without any noise"[1].

John Floyer in 1698 defined asthma as "laborious respiration with lifting of the shoulders and wheezing with intermittent episodes" and that the treatment needs rescue and controller therapy[1].

According to WHO estimate, 235 million people currently suffer from asthma. Asthma is the most common chronic disease among children. Asthma is a public health problem in all countries.

Most asthma-related deaths occur in low and lower-middle income countries. Asthma is under-diagnosed and under-treated [3].

ASTHMA- AN ALLERGY:

Asthma is a common chronic inflammatory disease of the airways characterized by airway hyper-responsiveness, which results in reversible increases in bronchial smooth muscle tone, variable amounts of inflammation of the bronchial mucosa, recurring symptoms, reversible airflow obstruction and bronchospasm[3]. Asthma is also characterized by episodic or chronic wheezing, cough and chest tightness.

Global Initiative for Asthma defines asthma as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment"[4].

SYMPTOMS

Common symptoms and signs of asthma include,

- Wheezing
- Coughing
- Breathing difficulty
- Tightness in the chest
- Worsening of symptoms at night
- Worsening of symptoms on exposure to cold air
- Appearance of symptoms while exercising
- Symptoms after exposure to allergens
- Increased heart rate >80 beats/min and
- FEV_1% and PEFR less than 80%.

Running nose, sinus infections, acid reflux disease, psychological stress and sleep apnea are the problems that can disturb with asthma management[4].

PATHOPHYSIOLOGY:

In a person with asthma, mucous exudates, goblet cell metaplasia, and epithelial basement membrane thickening obstruct the lumen of the bronchiole. In asthma the chronic inflammation of the airways results in increased contractility of the surrounding smooth muscles. The narrowing of the lumen is reversible with or without treatment in asthmatics[5].

The changes in the airways of the asthmatics also include an increase in eosinophils and thickening of the lamina reticularis. Chronically the airways smooth muscle may increase in size along with an increase in the number of mucous glands[5]. The association between allergy and asthma has been often recognized and plasma IgE levels are often elevated in asthma.

The eosinophils release proteins in the inflammatory reactions. These proteins may damage the respiratory airway epithelium and contribute to hyper-responsiveness. Leukotrines released from eosinophils and mast cells can enhance bronchoconstriction. Amines, neuropeptides, chemokines and interleukins have effects on contractility of the bronchial smooth muscle[6].

RISK FACTORS FOR ASTHMA:

The risk factors for asthma[7] are

- environmental factors like allergens
- tobacco smoking
- air pollutants
- occupational sensitizers
- respiratory infections
- host factors like airway hyper responsiveness
- family history of asthma and
- atopy.

GENETIC PREDISPOSITION IN ASTHMA:

Asthma can be caused by genetic predisposition. Burke W, Fesinmeyer M in his study found, family history as a predictor of asthma risk. The prevalence has increased considerably over the past 20 years, recent researches have suggested that the risk of allergies in young children is much greater when the mother is allergic than the father. The maternal inheritance of the allergies may be due to mother's antibodies influence on the child's immunity as it is developing in the womb[8].

Fernando Martinez in his study showed that the complex interactions between genetic and environmental factors help in the development of asthma. After birth, mother's milk contains antibodies and dietary substances that could alter infant's immunity and alter the risk of developing allergies in adult life. He also showed asthma was associated with positive family history [9].

Mathew A. C emphasized careful evaluation and long term follow up should be taken in children with low birth weight and a family history of asthma [10].

ASTHMA CLASSIFICATION:

On the basis of onset, asthma is classified into

- Childhood - onset asthma
- Adult-onset asthma
- Exercise-induced asthma
- Cough-induced asthma
- Occupational asthma

- Nocturnal asthma and
- Steroid-resistant asthma.

On the basis of severity of symptoms and signs, asthma is classified as

- Intermittent asthma
- Mild asthma
- Moderate asthma
- Severe asthma[11].

Global Initiative for Asthma (GINA) guidelines 2011 classified asthma based on FEV_1% and respiratory symptoms and exacerbations during day and night. Based on GINA guidelines, asthma patients were classified into three groups as

- Controlled
- Partly controlled and
- Uncontrolled group[4].

DIAGNOSING ASTHMA:

Asthma diagnosis are based on three components[11],

- Medical history
- Physical examination and
- Results from PFT by spirometer.

SPIROMETER

Spirometer is one of the equipments used for basic Pulmonary Function Tests (PFT's). Spirometry is a physiological and noninvasive test. It requires deep breaths and forceful expiration into a tube connected to a spirometer. Spirometry measures how an individual inhales or exhales volumes of air as a function of time.

Volume or flow is the important thing measured using spirometry[12]. The measurements are compared against standards developed for a person's age, height and weight measurements. The values below normal may indicate obstructed airways.

The bronchodilator drugs are given to open air passages before retesting with the spirometer. If the value improves after giving the drug there may the chance for asthma.

The spirogram will identify two different types of abnormal ventilation patterns, obstructive and restrictive. Obstructive patterns (eg. asthma, bronchitis) are one which affects the rate at which air can be expelled from the lungs and is characterized by a reduced forced expiratory volume in first second (FEV_1), normal forced vital capacity (FVC) and a low FEV_1%.

An FEV_1% of <70% is diagnostic of air flow obstruction and confirms obstructive disease. Restrictive pattern (eg. kyphosis, scoliosis, pulmonary fibrosis) affects lung expansion. FEV_1 and FVC are decreased, with a normal ratio of FEV_1/FVC[13].

Reversibility of FEV_1 by more than 12% suggests a diagnosis of asthma. Spirometer provides an assessment of severity, reversibility, variability, confirmation and diagnosis of asthma. The most common measurements are FVC, FEV_1, FEV_1%, and peak expiratory flow rate (PEFR).[14]

FEV_1 is the volume of forced vital capacity expired in 1st second of exhalation. FVC is the total volume expired forcefully with greatest speed and force after maximum inspiration. FEV_1% is the FEV_1 expressed as percentage of FVC. PEFR is the maximum velocity with which air is forced out of the airways during forced expiration.

ASTHMA TREATMENT AND MANAGEMENT:

There is no cure for asthma. The symptoms can be controlled with effective asthma treatment and management. Inhaled corticosteroids are taken daily to control the disease. Some inhalers contain both corticosteroid and a long-acting beta-agonist (LABA).

LABAs control symptom and help in opening the airways[15]. Agents that block synthesis of leukotrines or their cysLT_1 receptors are also used in the treatment of asthma.

Quick-relief medications are short-acting beta-agonists. Quick-relief medications do not control the disease. They are used to relax and open the airways and relieve symptoms during an asthma severity and are taken before exercise in asthma[15].

Acute asthma flare-ups or severe symptoms need both oral and intravenous corticosteroids. Proper treatment and management plan for asthma can reduce the symptoms and lead a better quality of life.

COMPLICATIONS OF ASTHMA

In the person with bronchial asthma from the childhood have certain developmental changes in the thorax because they need some extra effort to breathe. The sternum goes in and the ribs get lifted upward and forward called the pigeon chest.

In the status asthmaticus the patient fails to respond to the usual line of treatment. It is seen in chronic asthma patients. It is a life threatening complication and immediate hospitalization and emergency treatment is required.

AUTONOMIC NERVOUS SYSTEM AND ASTHMA:

The nervous system is the cornerstone to our ability to perceive, adapt to, and interact with the world around us. Part of this system is called the autonomic nervous system (ANS).

ANS regulates the activity of smooth muscle, cardiac muscle and certain glands[16]. ANS is a specific motor output portion of peripheral nervous system. ANS maintains internal homeostasis. Functions of ANS are studied by invasive and non invasive tests. Functions of ANS are affected by various factors.

Smooth muscles are present in the blood vessels and airways and line the tracts leading to outside of our body. The autonomic nervous system divides into two parts: the sympathetic nervous system and the parasympathetic nervous system.

The bronchioles and bronchi are innervated by ANS. Vagal stimulation causes bronchoconstriction and it is mediated by muscuranic receptors in bronchial tree. Sympathetic stimulation causes bronchodilatation and it is mediated by β_2 receptors in bronchial epithelium and smooth muscle.

In normal airways, the breathing is due to normal ANS function. In asthmatic airways, there is sometimes an imbalance favoring the parasympathetic system and it produces constriction of the airways and increased mucus secretion[17].

Sympathetic system increases the heart as a pump whereas parasympathetic stimulation decreases heart pumping allowing the heart to rest. Sympathetic stimulation increases overall activity of heart. This is accomplished by increasing both rate and force of contraction. Parasympathetic stimulation causes mainly opposite effects- decreased heart rate and strength of contraction[18]. VIP mediates dilatation of bronchi. Total airway resistance also plays a part in asthma.

HISTORY OF HEART RATE VARIABILITY:

The science of heart rate variability (HRV) was first identified in 1960's. HRV has wide use in cardiology. For the past 20 years, this technique has numerous studies and updates.

HRV provides knowledge about alteration in autonomic nervous system. HRV measurements exactly pinpoint sympathetic profile of an individual[19].

In 1965, Hon and Lee[20] noted that there was an alteration in the interbeat intervals during fetal distress before any change occurred in heart rate itself.

Heart rate variability is a measure of the balance between sympathetic mediators and parasympathetic mediators of heart rate. Epinephrine and nor epinephrine are released from sympathetic nerve fibers. They act on the sino-atrial and atrio-ventricular nodes and increase the rate of cardiac contraction and facilitate conduction at the atrio-ventricular node.

Parasympathetic mediators of heart rate that is, the influence of acetylcholine released by the parasympathetic nerve fibers acting on the sino-atrial and atrio-ventricular nodes leading to a decrease in the heart rate and a slowing of conduction at the atrio-ventricular node[21].

Sympathetic mediators exert influence over longer time periods and are reflected in the low frequency power (LFP) of the HRV spectrum.

Vagal mediators exert their influence more quickly on the heart and principally affect the high frequency power (HFP) of the HRV spectrum (between 0.15Hz and 0.4 Hz). Thus at any point in time the LFP: HFP ratio represents the sympathovagal balance[21].

HEART RATE VARIABILITY

Heart rate variability has been established as a tool to study cardiac autonomic activity. The lower frequencies (LF) and higher frequencies (HF) of HRV have a stronger association to sympathetic activity and vagal outflow respectively[22].

Heart rate variability is the cardiac beat to beat variation. It is a physiological phenomenon occurs due to variation in cardiac activity during respiration[23].

The heart rate and its beat to beat variation depend on SA node discharge which is influenced by autonomic activities.HRV is the most sensitive indicator of autonomic function mainly for sympathovagal balance.

HRV provide data about the death in subjects with and without heart disease. There is no specific treatment available to improve the prognosis for patients with abnormal HRV[24]. A variety of linear, nonlinear, periodical and oscillation patterns are present in heart rate fluctuation.

HRV parameters can be analyzed in time and frequency domain methods. Time domain is easier to assess but finer variations are not better appreciated. The frequency domain measures distribution of magnitude of variation in different frequency bands in the frequency of 0.0-0.4 Hz.

HF (high frequency) is due to vagal stimulation during respiration and is used as an index for vagal modulation. On giving atropine or by doing vagotomy respiratory sinus arrhythmia can be abolished. The heart rate fluctuation during respiration is due to central inhibition of vagus.

LF components of HRV has oscillatory pattern with intervals of 10 seconds. It is commonly associated with fluctuation in blood pressure.VLF component changes heart rate due to thermoregulation and humoral and local factors[25].

Power spectral analysis of HRV is done by Fast Fourier Transform (FFT) and auto regressive (AR) modeling. FFT is a non parametric method and is used in voice analysis and vibration study analysis of short term HRV.

AR modeling is the parametric method and is the combination of auto regressive identification with power spectral estimation. Both FFT and AR modeling estimate the power spectral signals. The spectral components of frequency domain measures are total power (TP), low frequency (LF), high frequency (HF) and very low frequency (VLF). Ultra LF is seen in long term recordings.

Time domain methods measure variation in heart rate and determine the interval between successive normal complexes. Simple time domain variables calculated are the mean NN interval, the mean heart rate, the difference between the shortest and longest NN interval and the difference between night and day heart rate.

Statistical methods are used for cyclic intervals recorded for 24 hours. They include the parameters derived from direct measurements of NN intervals and parameters derived from difference between NN intervals. These measurements determine high frequency variation in heart rate.

Geometrical methods measure sample density distribution using Lorenz plot of NN or RR intervals. HRV triangular index measurement

is the integral of the density distribution divided by maximum of the density distribution. This method depends on both number and quality of NN intervals.

There are two types of HRV recordings,

- Short term 5 minutes HRV recording
- Day night long term HRV recording

HRV is used to assess cardio respiratory control systems. The artifacts and the abnormal heart beats recorded are removed before analysis. HF component of HRV indicates vagal tone and LF component of HRV indicates sympathetic tone. LF/HF ratio assesses sympathovagal balance. The peripheral vascular resistance exhibits intrinsic oscillation with low frequency and this oscillation can be influenced by thermoregulation.

VLF and TP power represent the sympathetic tone. VLF also represents humoral and thermoregulatory effects and also negative emotions and worries. The analysis of all HRV datas is essential for clinical evaluation. HRV data depends on various factors. HRV obtained from normal healthy individuals are considered as reference and used for diagnostic purposes.

CLINICAL APPLICATIONS OF HRV

- Decreased HRV is observed in cardiovascular diseases.
- Alterations are observed in HRV before the onset of symptoms in cardiac disease.
- It is used as prognostic stool in post myocardial infarction and cardiac transplantation.
- It is used in the surveillance of post infarction and diabetic patients.
- Gives information about autonomic balance.
- It is used to determine the susceptibility to develop autonomic dysfunction like hypertension.
- Decreased HRV is correlated with risk for sudden cardiac death in heart patients.
- During interventions like exercise and yoga, HRV is altered.

AIM AND OBJECTIVES

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AIM

The aim of our study is to investigate the autonomic imbalance in bronchial asthma patients using spectral analysis of heart rate variability (HRV).

OBJECTIVES

- To compare HRV of bronchial asthma patients and normal volunteers.
- To assess the cardiovascular risk in bronchial asthma patients using HRV.
- To do correlation analysis between HRV parameters and PFT among bronchial asthma patients.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

ASTHMA

The partial obstruction of bronchioles due to spastic contraction of the smooth muscles that result in extreme difficulty in breathing is called bronchial asthma. 3 to 5 % of human population contracts this condition at some point in their life time. The hyper sensitivity to foreign agents which result in bronchiolar contraction is the most common cause known[26].

Younger population contracts this disease due to allergic hypersensitivity. Pollen grains of the plants are the major source which constitutes the allergens. Older population is susceptible to irritants in the air.

In the allergic type of asthma, the formation of extremely abundant quantities of IgE antibodies produces hypersensitive reactions due to antigen antibody complex when they contract specific allergens. These IgE antibodies in question are attached to the lung interstitial mast cells.

The person who has bronchial asthma and has already developed IgE antibodies to the pollen inhales the allergen, it reacts with the antibodies which are attached to the mast cells in the lung interstitium. These mast cells inturn are made to release histamine, bradykinin, eosinophilic chemotactic factor, leukotrines, etc. These three substances i.e., leukotrines, eosinophilic chemotactic factor and bradykinin constitute slow reacting substance of anaphylaxis.

Thus released substances result in edematous changes in the bronchiolar walls. This localized reaction induces thick mucus secretion and smooth muscle spasm in the bronchioles. Outcome of these events is the airway obstruction due to increased resistance.

The diameter of the bronchiolar lumen in bronchial asthma is less during expiration than inspiration, because bronchiolar collapse during expiratory effort compresses the bronchioles.

In a person with bronchial asthma inspiration is less taxing but the real difficulty comes in expiration. When the lung volumes are measured clinically the maximum expiratory rate is severely reduced and the timed expiratory volume is also affected resulting in breathlessness.

In an asthmatic episode the residual volume of the lung is enhanced so does the functional residual capacity. The thoracic cavity bulges resulting in permanent enlargement. This condition is called barrel chest[26].

CARDIAC ASTHMA

When the person with congestive cardiac failure has wheezing, coughing and shortness of breath, cardiac asthma is the likely diagnosis. The symptoms of cardiac asthma resembles bronchial asthma hence the name.

Cardiac asthma may be symptom of acute heart failure leading to pulmonary edema. It is very important to differentiate two types of asthma because the treatment of bronchial asthma could worsen cardiac asthma and leads to severe arrhythmias[27].

ATOPIC ASTHMA

Atopic asthma is characterized by chronic inflammation of the bronchial mucosa in which eosinophils and immunoglobulin (Ig)-E dependent mechanism is prominent.

The specific proeosinophilic mediator interleukin (IL)-5 and essential cofactor for IgE in B-lymphocytes play important role in atopic asthma and determine asthma clinical expression and severity which lead to development of interleukin targeted therapies[28].

Acupuncture is the most common treatment most population believes and it improves the pulmonary functions of the asthmatics with different state of disease[29].

AUTONOMIC NERVOUS SYSTEM:

ANS controls emotional responses of the body and responses to environment that occur without conscious knowledge. The striking characteristics of ANS are the rapidity and the intensity with which it changes the visceral functions.

The term “autonomic” is derived from the words auto and nomos. The meaning of auto is ‘self’ and nomos is ‘control’. The ANS controls functions of the involuntary organs of the body that includes heart, blood vessels, exocrine, endocrine glands and visceral organs[30].

The ANS is activated mainly by centers located in spinal cord, brainstem and hypothalamus. Cortical areas controlling functions of ANS are mainly limbic cortex and prefrontal cortex and the sympathetic response to emotion originates in these areas.

FUNCTIONS OF ANS

The five important functions of ANS are

- Homeostasis maintenance in the body
- Visceral activities regulation
- Smoothens body response
- Coordination of body response
- Assistance to endocrine system

DIVISIONS OF ANS

Sympathetic nervous system and parasympathetic nervous system are two branches of ANS. Enteric nervous system is considered as third division of ANS. Sympathetic division acts during stress responses i.e., flight or fight reactions and it is considered as the accelerator. The parasympathetic division of ANS functions during resting conditions and acts as the brake.

Sympathetic system helps the body to face and overcome critical situations in life. It helps in regulation of blood pressure, respiration, and metabolism. The cell bodies of sympathetic system are located in the intermediolateral grey horn first thoracic to 3rd or 4th lumbar segments of spinal cord and sympathetic ganglia close to vertebral column. Hence it is called as thoracolumbar division of the ANS[31].

The parasympathetic system works by the side of the sympathetic system. It checks the over activity of sympathetic system and smoothens the autonomic responses. It is called as craniosacral division of ANS because of its cell bodies location in the cranial nuclei in the brainstem and sacral region of spinal cord.

In most organs both these systems are activated in a reciprocal fashion i.e. when the discharge rate in one division is increased, the rate of discharge in other division is decreased. In some organs both division of ANS work synergistically like in stomach parasympathetic division increases the gastric secretion, simultaneous sympathetic activation causes increased mucus secretion.

Enteric nervous system is located within the walls of digestive tract. Two organized nerve plexus of this system are myentric plexus in between muscular coats involves in control of digestive tract motility and submucus plexus in submucus layer which regulates gastrointestinal blood flow[32].

NEUROTRANSMITTERS OF ANS

Preganglionic cholinergic sympathetic fibers secrete acetylcholine while postganglionic adrenergic sympathetic fibers secrete adrenaline and noradrenaline. Parasympathetic division secretes acetylcholine in both pre ganglionic and post ganglionic fibers.

HYPOTHALAMUS AND ANS

Hypothalamus has projections to the parasympathetic vagal nuclei and neurons in the medulla. Medulla has a group of nerve fibers which descend to the sympathetic nervous system in the spinal cord. Because of these connections, hypothalamus controls the heart rate, cardiac functions and vasoconstriction.

Hypothalamus integrates somatosensory, endocrine and autonomic responses that are essential components of homeostasis mechanisms during stressful conditions. Because of its influence on ANS, Sherrington pointed out that hypothalamus is the 'head-ganglion' of autonomic nervous system[33].

AUTONOMIC NERVOUS SYSTEM AND ASTHMA:

Parasympathetic nervous system when stimulated constricts the bronchioles, where as the sympathetic nervous system relaxes. In bronchial asthma there is an autonomic imbalance where the parasympathetic nervous system takes the upper hand. This invariably results in the constriction of airways[17].

The dominant hand played by the parasympathetic nervous system induces acetylcholine release from the nerve endings. This inturn acts on the postjunctional muscarinic receptors located on the smooth muscle and submucosal glands of the airways and cause constriction of bronchioles and excess mucus secretion[18].

ASTHMA AND CARDIOVASCULAR DISEASE

Paul L.Enright et al in their study found that 6% of people with cardiovascular diseases (CVD) or risks had previous history of asthma and 30% of them were taking asthma medications. They found people who were asthmatics with congestive heart failure had higher level of high density lipoprotein (HDL) cholesterol and plasma fibrinogen levels[34].

Michela Bellocchia et al in their study on predictors of cardiovascular disease in asthma and chronic obstructive pulmonary diseases (COPD) indicated that CVD are frequent in patients with chronic obstructive disorders and their strongest predictors were age and airway obstruction. They found the prevalence of pressure overload and volume overload were similar in both asthma and COPD[35].

Carlos Iribarren et al in their study on asthma in the older population found people with coronary heart disease, cerebrovascular disease and heart failure had bronchial asthma history particularly in women. They found asthmatics on corticosteroid medications were at risk of developing CVD[36].

SPIROMETRY

Spirometry is the most common procedure used to assess the ventilatory functions of lung as a function of time. It is the screening test for general respiratory health. The person subjected to spirometry need to give their maximum effort. This test is used to identify the obstructive and the restrictive ventilation patterns.

HISTORY OF SPIROMETRY

The history of concept of spirometer started with Roman Empire. Claudius Galen, the Greek doctor performed the lung function test by asking a boy to breath in and out of the bladder[37].

Air volumes of the lungs were measured by J.Jurin and he had given absolute volumes. Tidal volume of 600 ml and maximal expiration of 3610 ml were measured. The principles of Archimedes were used in doing this procedure with help of the bladder and were asked blow into it[37].

At the beginning of 19th century, Sir Humphry Davy measured his own volumes and capacities with the help of a gasometer. He

used hydrogen dilution method to measure residual volume but now helium is used instead of hydrogen.

Gasometer was a complex instrument with a counter weight to balance. Sir Humphry Davy was the first person to estimate his own oxygen consumption and carbon-dioxide (CO_2) liberation [38].

E.Kentish and Charles Turner used pulmometer to measure ventilatory volumes and the power of expiratory muscles. Karl Von Vierordt used expirator to measure lung volumes by focusing exhaled gases and found exact determinants of volumetric parameters[39].

John Hutchinson was the first to invent spirometer which captures exhaled air from the lungs and measure vital capacity. Wintrich developed a spirometer which was easier to use. He found that body weight, height and age determine vital capacity[40].

The portable spirometer was made by E.Smith and with this gas metabolism was quantified by Him. A kymograph was added to the spirometer by Salter and recorded the time in relation to ventilatory volumes.

Ergospirometery, Pneutachygraphic spirometer, vitallograph and Jaeger spirometer were also used to measure ventilatory volumes. Modern spirometry has closed circuit and open circuit methods.

The person breathes into a container which was already filled and through soda lime tower the exhaled air passes which absorbs CO_2 and oxygen goes back into the container in the closed circuit method. The energy expenditure could not be measured during physical activity by closed circuit method[41].

The person breathes air from outside and expired air enters into a gasometer. The expired air is measured and analyzed. It is useful during physical activity to measure the loss of the energy.

There are three open circuit methods. In portable spirometry expired air passes through gasometer which was analyzed and oxygen consumption determined. In the bag technique the expired air was collected in the canvas bag or the rubber balloon[41].

In the computerized spirometry the expired air of the subject is continuously sampled. There is flow measuring device to record air flow. The expired gas mixture composition is analyzed for oxygen and carbon dioxide.

HEART RATE VARIABILITY

Heart Rate Variability has emerged as the most common tool to assess sympathovagal balance in humans either for research or for clinical studies.

There are more publications on HRV during past ten years. HRV is the interval between two R waves. More the variability between RR intervals more healthy is the heart functioning.

There is an association between death due to cardiac cause with increase in sympathetic and decrease in parasympathetic activity. This has emerged as useful marker in identifying the autonomic dysfunction.

HRV is one of the most important markers of sympathetic balance. Other names for HRV are Cycle Length Variability, RR Variability and RR interval tachogram. HRV is the most commonly used term[23].

HISTORY OF HRV

In 1965, Hon and Lee gave appreciation for HRV and its clinical relevance and noted that there was alterations in the interbeat intervals during fetal distress before any change occurred in heart rate itself[20].

The clinical importance of HRV became appreciated in the late 1980s, when it was confirmed that HRV was a strong and independent predictor of mortality after an acute myocardial infarction.

With the availability of new, digital, high-frequency, 24-hour, multichannel ECG recorders, 5 min, HRV has the potential to provide additional valuable insight into physiological and pathological conditions and to enhance risk stratification[42].

The theory based on the role of HRV in understanding the nature of vagal outflow to the heart decomposes HRV based on frequency

domain with an emphasis on respiratory sinus arrhythmia and its transmission by a neural pathway that is distinct from other components of HRV.

PHYSIOLOGICAL BASIS OF HRV

Heart rate variability has been established as a tool to study cardiac autonomic activity. The lower frequencies (LF) and higher frequencies (HF) of HRV have a stronger association to sympathetic activity and vagal outflow respectively[43].

Heart rate variability is the cardiac beat to beat variation. It is a physiological phenomenon occurs due to variation in cardiac activity during respiration[23].

The heart rate and its beat to beat variation depend on SA node discharge which is influenced by autonomic activities.HRV is the most sensitive indicator of autonomic function mainly for sympathovagal balance.

HRV provide data about the death in subjects with and without heart disease. There is no specific treatment available to improve the prognosis for patients with abnormal HRV[24]. A variety of linear, nonlinear, periodical and oscillation patterns are present in heart rate fluctuation.

HRV parameters can be analyzed in time and frequency domain methods. Time domain is easier to assess but finer variations are not better appreciated. The frequency domain measures distribution of magnitude of variation in different frequency bands in the frequency spectrum of 0.0-0.4 Hz.

HF (high frequency) is due to vagal stimulation during respiration and is used as an index for vagal modulation. On giving atropine or by doing vagotomy respiratory sinus arrhythmia can be abolished. The heart rate fluctuation during respiration is due to central inhibition of vagal tone.

LF components of HRV has oscillatory pattern with intervals of 10 seconds. It is commonly associated with fluctuation in blood

pressure.VLF component changes heart rate due to thermoregulation and humoral and local factors[25].

Power spectral analysis of HRV is done by Fast Fourier Transform (FFT) and auto regressive (AR) modeling. FFT is a non parametric method and is used in voice analysis and vibration study analysis of short term HRV.

AR modeling is the parametric method and is the combination of auto regressive identification with power spectral estimation. Both FFT and AR modeling estimate the power spectral signals. The spectral components of frequency domain measures are total power (TP), low frequency (LF), high frequency (HF) and very low frequency (VLF). Ultra LF is seen in long term recordings.

Time domain methods measure variation in heart rate and determine the interval between successive normal complexes. Simple time domain variables calculated are the mean NN interval, the mean heart rate, the

difference between the shortest and longest NN interval and the difference between night and day heart rate.

Statistical methods are used for cyclic intervals recorded for 24 hours. They include the parameters derived from direct measurements of NN intervals and parameters derived from difference between NN intervals. These measurements determine high frequency variation in heart rate.

Geometrical methods measure sample density distribution using Lorenz plot of NN or RR intervals. HRV triangular index measurement is the integral of the density distribution divided by maximum of the density distribution. This method depends on both number and quality of NN intervals. There are two types of HRV recordings,

- Short term 5 minutes HRV recording
- Day night long term HRV recording

HRV is used to assess cardio respiratory control systems. The artifacts and the abnormal heart beats recorded were removed before analysis. HF component of HRV indicates vagal tone and LF component of HRV indicates sympathetic tone.

LF/HF ratio assesses sympathovagal balance. The peripheral vascular resistance exhibits intrinsic oscillation with low frequency and this oscillation can be influenced by thermoregulation.

VLF and TP power represent the sympathetic tone. VLF also represents humoral and thermoregulatory effects and also negative emotions and worries. The analysis of all HRV datas is essential for clinical evaluation. HRV data depends on various factors. HRV obtained from normal healthy individuals are considered as reference and used for diagnostic purposes[44].

HRV AND ASTHMA

Kuzma N et al, in the study of seasonal variation in HRV in asthmatic children found that the environmental changes during different seasons increase the symptoms in the asthmatics. HRV of the asthmatic children is more susceptible to seasonal changes. They found there was seasonal variation in high frequency (HF), low frequency (LF) and LF/HF ratio of the HRV components which have been used as an index for autonomic functions[45].

Domnik NJ, et al, in their study of induced hyper responsiveness altered HRV and body temperature found that there was an altered autonomic tone in chronic respiratory diseases and suggested it as an important factor in cardiovascular co-morbidities. They also found mild allergic sensitization in asthma was associated with reduced HRV[46].

Lutfi MF et al, in their study of autonomic modulation in patients with bronchial asthma based on short term HRV said that the level of asthma control correlate positively with normalized LF and LF / HF ratio and negatively with normalized HF of HRV. They found duration of asthma correlates positively with HF norm and negatively with LF norm. They concluded poor asthma management is associated with lower HRV, depressed sympathetic tone and enhanced parasympathetic effect especially with longer asthma duration[47].

Sekerel BE, et al the study of effects of inhaled formeterol on ANS in adolescents with asthma found that inhalation of single dose formeterol increased heart rate and decreased HRV during first 12 hours and concluded that there was decreased cardiovagal responsiveness and increased sympathetic tone in cardiac autonomic control[48].

Chen SR et al, in their study of the influence of physical activity level on HRV among asthmatics found that total power, LF, LF norm and LF/HF ratio of HRV parameters were significantly low in asthmatics compared to healthy adults both in the resting condition and during physical activity. They found that physical activity had positive relationship with LF norm and negative relationship with HF norm in asthmatics. They suggested engaging asthmatics with moderate physical activity improves HRV[49].

Campbell TS et al, in their study on asthma self-efficacy, high frequency HRV and negative effect in daily life of the asthma, suggested that severe asthma was associated with increased parasympathetic activity and airflow obstruction. They suggested physical activity was associated with decreased levels of high frequency HRV in asthmatics[50].

Du J, et al in the study of HRV in asthma showed that in asthma subjects the vagal tone were increased and sympathetic tone were decreased compared to that of normal persons. They suggested autonomic nervous function of asthmatic differ from young adults even in the normal conditions[51].

Korematasu S, et al in their study of auto regressive analysis of HRV and blood pressure (BP) in asthmatic children found parasympathetic nervous system disorder in severe asthmatics and concluded that the spectral analysis of HRV and BP are the useful tool for quantifying ANS activity[52].

Mitsunori Murata, et al in their study of HRV during 24 hours in asthmatic children found that the autonomic nervous functions in asthmatics were decreased and said that severity of asthma had significant effects on HRV. They also suggested that autonomic functions in asthmatic differ from normal subjects even when they were free from asthma attacks[53].

Gupta J, et al in the study of HRV in bronchial asthma found normalized LF component was significantly reduced while normalized HF component was significantly increased in asthmatics. They concluded there was significant rise in vagal outflow and decreased sympathetic effects in asthmatics and this may be the patho-physiological mechanism for airway obstruction in bronchial asthma[54].

Gomes EL, et al in the study of autonomic modulation during maximal and sub maximal work rate and functional capacity in asthmatic children suggested that there was no withdrawal of parasympathetic cardiac modulations after maximum exercise while the functional capacity and lung function vary depending on the degree of the inflammation of the airways in the asthmatics[55].

Emin O[56], et al in their study on ANS dysfunction and atopic asthma disease severity in younger population found ANS dysfunction varied significantly among mild, moderate and severe asthmatics. They found HRV and sympathetic skin response provide platform for assessing the severity of asthma in the younger age groups.

Ostrowska Nawarycz L et al, in their study of HRV analysis in younger population with bronchial asthma confirmed that there was significant association between the vagal activity and frequency and intensity of bronchial asthma in children and youth and insisted short term HRV could be used to assess autonomic function in these people[57].

Jartii TT et al, in the study of cardiovascular autonomic functions of cardiovascular system in asthmatic children by spectral analysis of HRV and B.P found alterations in systolic B.P and an increase in sympathetic functions in CVS of the children with asthma[58].

Garrard CS et al, in the study of spectral analysis of HRV in bronchial asthma found that acute asthmatics had higher heart rates and HRV due to sympathetic mediation compared to that of normal subjects[59].

MATERIALS

AND

METHODOLOGY

MATERIALS AND METHODS

This study was done in the department of Physiology, PSG IMS&R. Institutional Human Ethics Committee ethical clearance and informed written consent from the cases and controls were obtained before the study.

This was an observational type of study.

30 cases and 30 controls were included in the study.

The cases were persons having bronchial asthma in the age group between 20 to 45 years. The cases were selected from pulmonology OPD and respiratory medicine OPD according to the inclusion criteria.

Details of present history, treatment history were obtained. The controls were normal healthy volunteers in the same age group. General examinations including height in cms and weight in kgs were recorded.

INCLUSION CRITERIA:

- Physician diagnosed asthmatics as cases.
- Age between 20-45 years includes both men and women.
- Normal persons willing to participate in the study as controls.

EXCLUSION CRITERIA:

- Smokers
- Alcoholics
- Hypertensive patients
- Diabetic patients
- Patients with thyroid disorders
- Ischemic heart disease & myocardial infarction patients
- Patients with lung cancer and restrictive lung diseases
- Pregnancy
- Patients on drugs known to influence HRV within 24hrs prior to recruitment**.**

The DATA collection tool is a protocol that has patient data, history, physical examination findings and investigation details which is attached in annexure. The subjects who fulfilled the criteria were taken for ECG recording for HRV analysis in the Physiology research laboratory, and pulmonary function tests in the PFT laboratory, PSG IMS&R.

PULMONARY FUNCTION TESTS

PFTs are employed to assess the ventilation, diffusion and perfusion of the lungs. Ventilatory function measures lung size, patency of airways and alveolar ventilation. PFTs are employed to reach a diagnosis, to follow the progression of the disease and the effectiveness of treatment, to assess respiratory status and to assess physical fitness.

SPIROMETRY

PFT is the non invasive physiological test. Spirometry is the most common laboratory procedure used to assess the ventilatory functions of lung as a function of time. It is the screening test for general respiratory health.

Premedication test was done for both cases and controls. Those persons having normal PFT values were taken as controls. Post medication test was done after giving asthalin (salbutamol 400mcg) nebulizer and rest for about 30 min in the cases. Those persons who had reversibility of FEV_1 by more than 12% were diagnosed as asthmatics and they were included in the study.

While performing spirometry, the subject must give his maximum effort. The procedure was carefully and clearly explained to cases and controls and actively motivated to perform maximally. During spirometry the subjects were asked to sit in a chair straight and both sole touching the floor flat. The procedure needs time to get the maximum effect.

The two obstructive and restrictive abnormal ventilation patterns are identified using spirogram. Obstructive patterns are one which affects the rate at which air can be expelled from the lungs and is characterized by a reduced forced expiratory volume in first second (FEV_1), normal or reduced forced vital capacity (FVC) and a low FEV_1%.

The FEV_1% of <70% is diagnostic of air flow obstruction and confirms obstructive disease. Restrictive pattern affects lung expansion. FEV_1 and FVC are decreased, leaving a normal ratio of FEV_1/FVC.

THE INSTRUCTIONS GIVEN TO THE SUBJECTS DURING THE PROCEDURE:

- Seal the lips and teeth tightly around the mouthpiece.
- Breathe in fully so the lungs must be completely full.
- Nose clips are applied to the nose.
- Blow the air out as fast as possible for minimum of 6 seconds with maximal effort.
- Breath in fully again without removing the mouthpiece from the mouth.

The controls and cases were asked to do the spirometry thrice and the best of the three readings was included for the study. Spiropalm-digital airflow spirometry which senses air current connected to a computer is used to assess pulmonary function tests. The variables of PFTs taken in the study are forced vital capacity (FVC), forced expiratory volume in first second (FEV_1), FEV_1%, Peak expiratory flow rate (PEFR) and $FEF_{25-75\%}$.

- **FORCED VITAL CAPACITY**

FVC is the largest amount of air that can be expired after a maximal inspiration.

It is an index for pulmonary function and assesses the strength of the respiratory muscle.

- **FORCED EXPIRATORY VOLUME IN FIRST SECOND**

FEV_1 is the fraction of vital capacity expired during the first second of a forced expiration.

It is decreased in asthma.

- **FORCED EXPIRATORY VOLUME IN FIRST SECOND PERCENT**

$FEV_1\% = FEV_1/FVC \times 100$

Normal is 80%. It is useful to differentiate obstructive and restrictive disease.

- **PEAK EXPIRATORY FLOW RATE**

It is the maximum flow rate of air during a single forced expiration.

It is useful in distinguishing reversible and irreversible lung diseases.

- **$FEF_{25-75\%}$:**

This is the flow rate between 25% and 75% 0f FVC.

It is useful for detecting the response of the bronchodilator in the asthmatics

ECG RECORDING AND HRV ANALYSIS

HRV is a non-invasive procedure. Electrocardiograph was done for 5 minutes in a computerized physiograph (NEVIQURE- Digital ECG recorder) in Lead 2. HRV analysis was done using Finland software.

ECG RECORDING

After getting written informed consent for ECG recording all the study subjects were enrolled. To avoid anxiety the subjects were asked to sit silently for few minutes before the procedure in Physiology laboratory. ECG recording was done in supine position by using computerized physiograph in Lead II for a period of 5 minutes with the use of adhesion electrodes in both wrist and legs.

The left arm was connected with positive electrode, right arm with negative electrode, left foot with reference electrode and right foot with ground electrode. Baseline ECG recording were obtained from all the subjects and abnormal baseline ECG were excluded.

RR intervals were recorded after clearance of noise and baseline fluctuations by digital filters. Subjects with ectopic beats were excluded from the study. Resting heart rate was recorded. All the data were filtered by using a digital notch filters with a sampling of 1000 samples/sec.

The inbuilt software select the RR peaks and these RR intervals which were recorded as time points were then introduced into a Microsoft excel sheet and RR intervals were copied to a notepad file.

The resting autonomic activity was assessed by HRV. Two types of parameters are determined by HRV analysis which includes,

1. Time Domain parameters
2. Frequency Domain parameters.

THE TIME DOMAIN PARAMETERS:

The Time Domain parameters are based on statistical operations on R-R intervals. Mean RR (NN), standard deviation of all NN intervals (SDNN), the square root of the mean squared difference of successive NNs (RMSSD), PNN50-the proportions of NN50 divided by total number of NNs and NN50 are the parameters. They are used to distinguish two different HRV indices.

- **Mean RR (NN):**

This is the average of all NN intervals. It indicates sympathovagal function because it is inversely proportional to mean heart rate at a given physiological state.

It is also called as normal to normal intervals.

- **SDNN**

It is the standard deviation of all NN intervals. This is a measure of total variability.

It reflects HRV in low and high frequency ranges, when considered for a short period of time.

- **NN50 count:**

This estimates high frequency variation in heart rate.

It is the number of pairs of adjacent NN intervals differing more than 50 ms in the entire recording.

- **pNN50**

  It is the proportion derived by dividing NN50 by total number of NN intervals. This estimates high frequency variation in heart rate along with NN50 count.

- **RMSSD**

  It is the square root of the mean of the sum of the squares of differences between adjacent NN intervals. This also estimates high frequency variations in heart rate and hence it is a measure of vagal response.

The Frequency Domain Measures:

In HRV recorded all abnormal heartbeats and artifacts were removed. Cardiac tachogram was resampled. The frequency domain parameters are LF, HF. LF nu, HF nu and LF/HF power ratio. Other parameters include total power and very low frequency power.

- **Low frequency power (LF)**

  LF spectrum is in the range from 0.04 to 0.15 Hz.

  This indicates both sympathetic and parasympathetic tone.

- **High frequency power (HF)**

  HF power spectrum is in the range from 0.15 to 0.4 Hz.

  This indicates vagal tone.

- **LF norm** (nu)

  It is low frequency power in normalized units.

  LF norm = LF/ (Total power – VLF) X100

- **HF norm (nu)**

  It is high frequency power in normalized units.

  HF norm = HF/ (Total power – VLF) X100

- **LF/HF power ratio:**

  The LF/HF ratio is used to asses sympathovagal balance. A decrease in the score indicates either decrease in sympathetic tone or increase in parasympathetic tone.

HRV analysis was done by feeding these harmonic components of RR interval notepad file to HRV analysis software version 1.1 from Biomedical Signal Analysis group, Department of Applied Physics, University of Kuopio, Finland.

Power spectral analysis was done by fast Fourier transformation, discovered by Jean Baptiste Joseph Fourier.

STATISTICAL ANALYSIS

The statistical analysis was done using SPSS software (statistical package for the social science version-19). By independent Students t' test, analysis was done between the study group and control group.

Both HRV and PFT values were compared, which gave the exact relationship between HRV and asthma.

Pearson correlation analysis was used to correlate HRV parameters and FEV_1% and PEFR. Chi square test was used to correlate family history with bronchial asthma.

Values were expressed as Mean ± SD.

$p > 0.05$ was considered not significant.

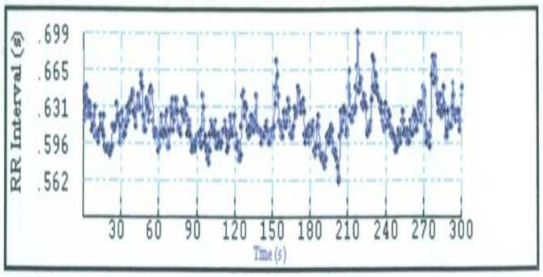
$p \leq 0.05$ was considered statistically significant.

$p < 0.01$ was considered moderately significant.

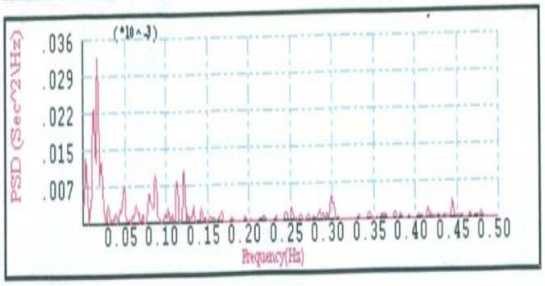
$P < 0.001$ was considered highly significant.

Heart Rate Variability Analysis

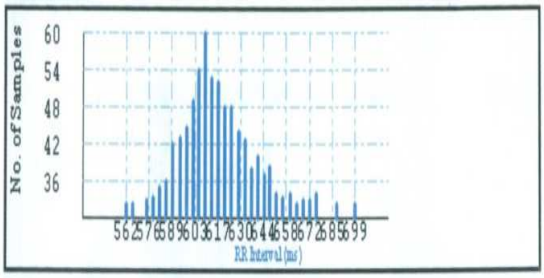
RR TachoGram:



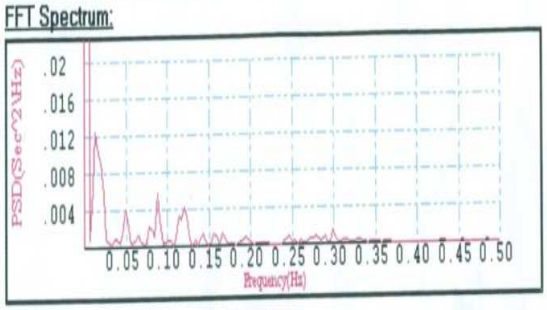
Lomb Periodogram Spectrum:



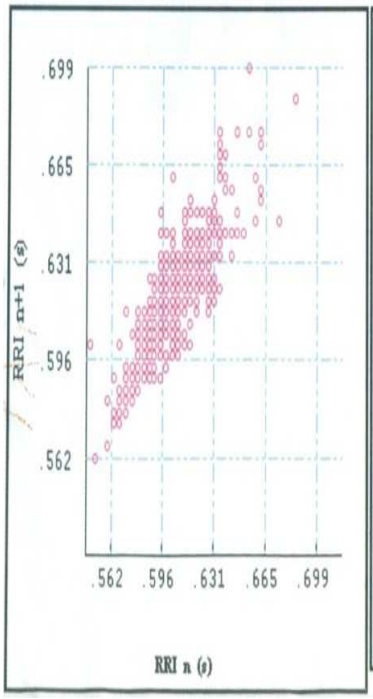
HistoGram:



FFT Spectrum:



Poincare Plot:



Data Statistics:

Parameter	Value
Max RR	0.699 s
Min RR	0.562 s
Max/Min	1.244
Mean RR	0.616 s
Max HR	107 bpm
Min HR	86 bpm
Mean HR	97 bpm

Parameter	Value
SDNN	19.473 ms
RMSSD	11.234
NN50	0 count
pNN50	. %
Variance	379.21 ms^2
Sample Points	484
Range	299

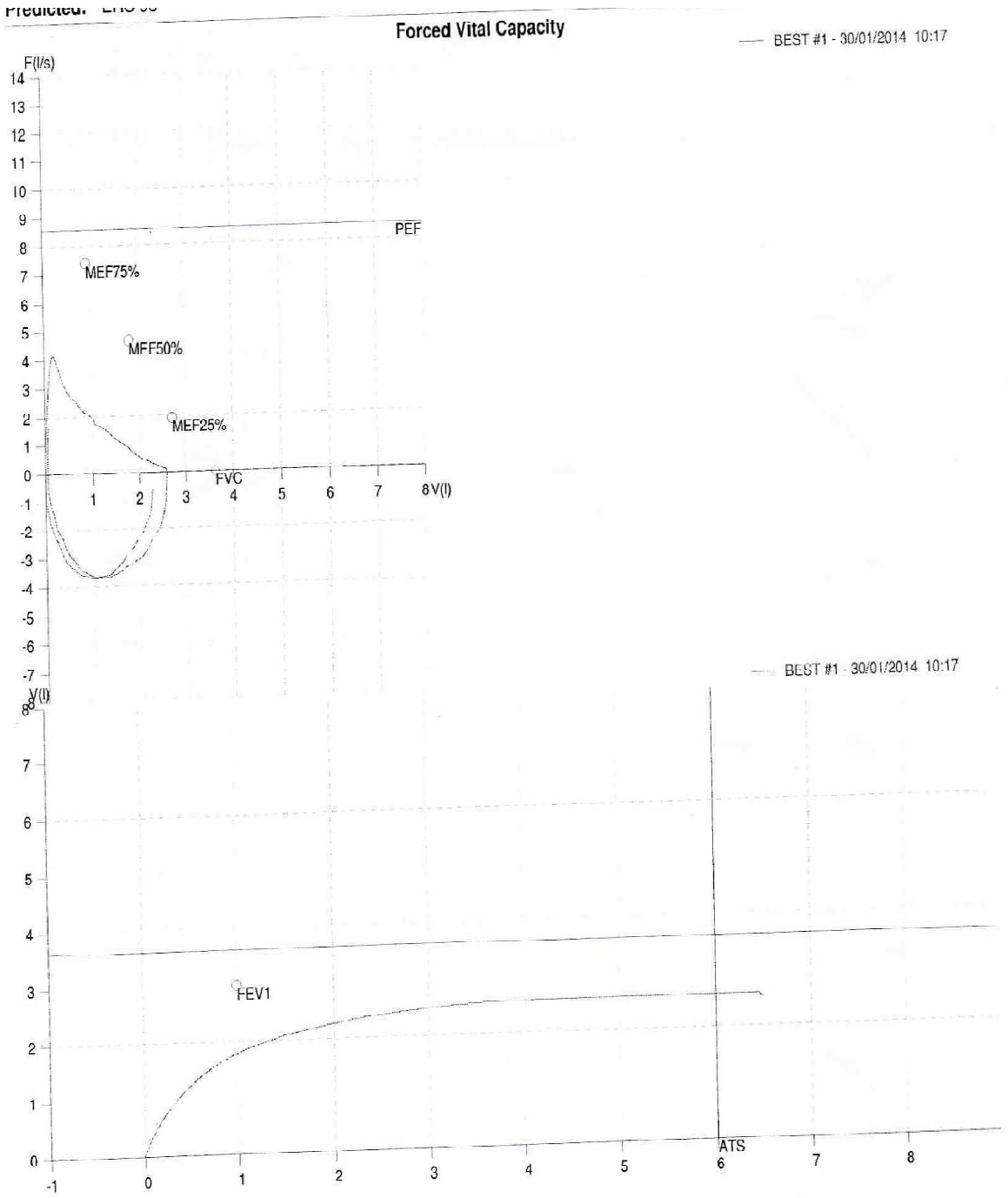
Lomb Frequency Statistics:

	Range (Hz)	Power(%)	Power(n.u.)	Power(ms^2
VLF	0.0 - 0.04	44.4		332
LF	0.04 - 0.15	35.5	63.8	265
HF	0.15 - 0.4	20.2	36.3	151
LF/HF		1.757		

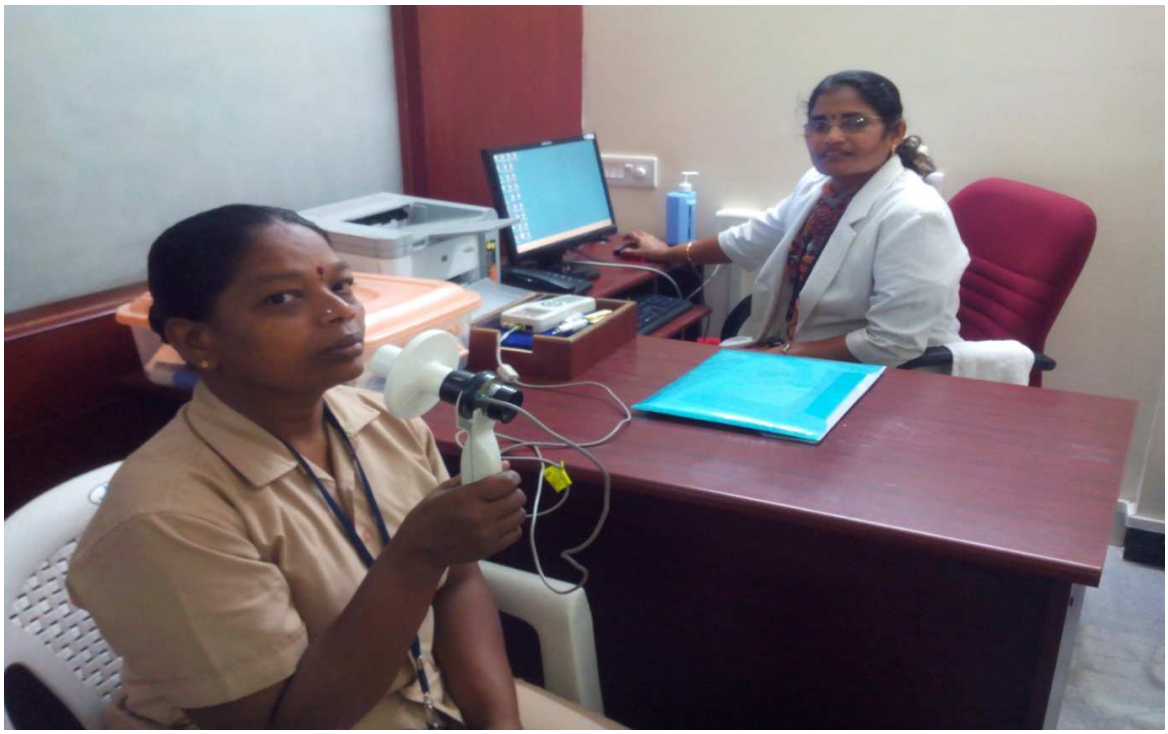
FFT Frequency Statistics:

	Range (Hz)	Power(%)	Power(n.u.)	Power(ms^2
VLF	0.0 - 0.04	40.8		42
LF	0.04 - 0.15	40.3	68.1	41
HF	0.15 - 0.4	18.9	31.9	21
LF/HF		2.132		

Predicted:


Forced Vital Capacity
BEST #1 - 30/01/2014 10:17
F(l/s)
PEF
MEF75%
MFF50%
MEF25%
FVC
V(l)
BEST #1 - 30/01/2014 10:17
V(l)
FEV1
ATS

Parameter	UM	Description	Pred.	LLN	BEST#1	%Pred.
Best FVC	l(btps)	Best Forced Vital Capacity	3.47	2.78	2.24	64
Best FEV1	l(btps)	Best Forced Exp Volume in 1 sec	3.01	2.41	1.16	38
Best PEF	l/sec	Best Peak Expiratory Flow	6.87	5.49	3.15	46
FVC	l(btps)	Forced Vital Capacity	3.47	2.78	2.24	64
FEV0.5	l(btps)	Forced Exp Volume in 0.5 sec			0.80	
FEV1	l(btps)	Forced Exp Volume in 1 sec	3.01	2.41	1.16	38
FEV2	l(btps)	Forced Exp Volume in 2 sec			1.57	
FEV3	l(btps)	Forced Exp Volume in 3 sec			1.82	
PEF	l/sec	Peak Expiratory Flow	6.87	5.49	3.15	46
FEV6	l(btps)	Forced Exp Volume in 6 sec	3.74	2.99	2.20	59
PIF	l/sec	Peak Inspiratory Flow			3.05	
FEV1/FVC%	%	FEV1 as % of FVC	82.8	66.3	51.9	63
FEV2/FVC%	%	FEV2 as % of FVC			70.2	
FEV3/FVC%	%	FEV3 as % of FVC			81.1	
FEV6/FVC%	%	FEV6 as % of FVC			98.1	
FEV1/FEV6%	%	FEV1 as % of FEV6			52.8	
FEF25-50%	l/sec	Mid-exp flow between 25-50%FVC			0.90	
FEF25-75%	l/sec	Forced mid-expiratory flow	3.84	3.07	0.54	14
FEF50-75%	l/sec	Mid-exp flow between 50-75%FVC			0.39	
FEF75-85%	l/sec	Mid-exp flow between 75-85%FVC			0.21	
FEF0.2-1.2	l/sec	Mid-exp flow between 0.2-1.2 l			1.02	
MEF75%	l/sec	Max Exp Flow @ 25% FVC	6.02	4.82	1.36	23
MEF50%	l/sec	Max Exp Flow @ 50% FVC	4.33	3.46	0.62	14
MEF25%	l/sec	Max Exp Flow @ 75% FVC	2.00	1.60	0.27	13
FET100%	sec	Forced Expiratory Time			6.6	
IC	l(btps)	Inspiratory Capacity			1.65	
FIVC	l(btps)	Forced Insp. Vital Capacity			2.21	
FIF25-75%	l/sec	Forced mid-inspiratory flow			2.84	
t25	msec	MEF75 time			280	
t50	msec	MEF50 time			960	
t75	msec	MEF25 time			2440	
PEFr	l/min	Peak Expiratory Flow (l/min)	411.9	329.5	188.7	46



RESULTS

RESULTS

60 subjects were included in this study. Duration of the study was for 7 months from January to July 2014. 30 were normal subjects and 30 were bronchial asthmatics.

PFT and five minute electrocardiogram was taken for all the 60 subjects and HRV analysis was done.

The PFT values were compared between the controls and cases.

The HRV parameters (Time domain measures and the frequency domain measures) were compared between the controls and cases.

p value of < 0.05 was considered as significant.

Group I - Controls – normal subjects.

Group II - Cases – bronchial asthma patients.

Independent student t test, Pearson correlation analysis and Chi square test were used for statistical analysis.

1. BASELINE CHARACTERISTICS OF THE BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS (Table: 2 and Chart: 1)

Age (years)

Mean age of group I (Controls) was 31.27 ± 7.08 and group II (cases) was 32.03 ± 8.52. This increase in mean age of the cases was not statistically significant with p value of 0.706

Weight (kg)

Mean weight of group I was 62.4 ± 12.09 and group II was 60.8 ± 11.62.This decrease in mean weight of the cases was not statistically significant with p value of 0.603.

Height (cm)

Mean height of group I was 161.53 ± 11.07 and group II was 162.93 ± 9.56. This increase in mean height of the cases was not statistically significant with p value of 0.602.

BMI (kg/m^2)

Mean BMI of group I was 23.89 ± 2.85 and group II was 23.05 ± 3.19. This decrease in mean BMI of the cases was not statistically significant with p value 0.282.

2. COMPARISON OF PULSE AND BLOOD PRESSURE OF THE BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS (Table: 3 and Chart: 2).

Pulse rate (bpm)

Mean pulse rate of group I was 76.33 ± 7.26 and group II was 75.27 ± 5.47. This decrease in mean pulse rate of the cases was not statistically significant with p value 0.523.

Blood pressure (mmHg)

Mean systolic blood pressure (SBP) of group I was 120 ± 8.7 and group II was 112.33 ± 9.35. This decrease in mean SBP of the cases was highly significant with p value < 0.01.

Mean diastolic blood pressure of group I was 75 ± 9 and group II was 73 ± 7.49. This decrease in mean diastolic blood pressure of the cases was not statistically significant with p value < 0.354.

3. COMPARISON OF PULMONARY FUNCTION TESTS VALUES OF THE BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS

FVC (L) (Table: 4 and Chart: 3)

Mean FVC values of group I was 3.65 ± 0.82 and group II was 2.29 ± 0.70. This decrease in mean FVC of the cases was very highly significant with p value < 0.001.

FEV_1 (L) (Table: 4 and Chart: 3)

Mean FEV_1 values of group I was 3.11 ± 0.69 and group II was 1.56 ± 0.59. This decrease in mean FEV_1 of the cases was very highly significant with p value < 0.001.

FEV_1 % (Table: 4 and Chart: 4)

Mean FEV_1% values of group I was 84.82 ± 1.92 and group II was 63.74 ± 7.9. This decrease in mean FEV_1% of the cases was very highly significant with p value < 0.001

$FEV_{25-75\%}$ (L) (Table: 5 and Chart: 3)

Mean $FEV_{25-75\%}$ values of group I was 3.43 ± 0.42 and group II was 1.08 ± 0.5. This decrease in mean $FEV_{25-75\%}$ of the cases was very highly significant with p value < 0.001

PEFR (L/sec) (Table: 5 and Chart: 5)

Mean PEFR values of group I was 7.69 ± 1.25 and group II was 3.75 ± 1.79. This decrease in mean PEFR of the cases was very highly significant with p value < 0.001.

4. COMPARISON OF TIME DOMAIN MEASURES OF THE BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS

Mean RR (sec) (Table: 6 and Chart: 6)

Mean of the mean RR interval of group I was 0.74 ± 0.1 and group II was 0.81 ± 0.13. This increase in mean of the mean RR in the cases was statistically significant with p value < 0.05.

Mean HR (bpm) (Table: 6 and Chart: 7)

Mean of the mean HR of group I was 83.23 ± 8.7 and group II was 74.73 ± 6.97. This decrease in mean of the mean HR in the cases was very highly significant with p value < 0.001.

SDNN (ms) (Table: 7 and Chart: 8)

The mean SDNN of group I was 63.37 ± 27.75 and group II was 37.30 ± 18.59. This decrease in mean SDNN of the cases was very highly significant with p value < 0.001.

RMSSD (Table: 7 and Chart: 8)

The mean RMSSD of group I was 51.98 ± 15.59 and group II was 25.82 ± 9.33. This decrease in mean RMSSD of the cases was very highly significant with p value < 0.001.

NN50 counts (Table: 7 and Chart: 9)

The mean NN50 counts of group I was 72.57 ± 9.96 and group II was 37.77 ± 6.05. This decrease in mean NN50 counts of the cases was highly significant with p value < 0.01.

pNN50 % (Table: 7 and Chart: 9)

The mean pNN50% of group I was 27.06 ± 3.16 and group II was 12.90 ± 2.36. This decrease in mean pNN50% of the cases was very highly significant with p value < 0.001.

5. COMPARISON OF FREQUENCY DOMAIN MEASURES OF THE BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS

Very Low power frequency in ms^2 (Table: 8 and Chart: 10)

Mean VLF in ms^2 of group I was 2334.23 ± 520.20 and group II was 1289.36 ± 285.89. This decrease in mean VLF in ms^2 of the cases was highly significant p value < 0.01.

Low power frequency in ms^2 (Table: 8 and Chart: 11)

Mean LF in ms^2 of group I was 331.07 ± 64.27 and group II was 199.4 ± 35.27. This decrease in mean LF in ms^2 of the cases was very highly significant with p value < 0.001.

High power frequency in ms^2 (Table: 8 and Chart: 11)

Mean HF in ms^2 of group I was 85.9 ± 11.18 and group II was 143.23 ± 25.46. This increase in mean HF in ms^2 of the cases was very highly significant with p value < 0.001.

Low power frequency in normalized units (LF n.u) (Table: 9 and Chart: 12)

Mean LF n.u. of group I was 69.19 ± 9.72 and group II was 68.89 ± 11.82. This decrease in mean LF n.u. of the cases was not statistically significant with p value 0.236.

High power frequency in normalized units (HF n.u) (Table: 9 and Chart: 13)

Mean HF n.u. of group I was 30.78 ± 9.72 and group II was 33.47 ± 15.79. This increase in mean HF n.u. of the cases was not statistically significant with p value 0.107.

LF/HF ratio (Table: 9 and Chart: 13)

Mean LF/HF ratio of group I was 3.85 ± 0.37 and group II was 1.66 ± 0.24. This decrease in mean LF/HF ratio of the cases was not statistically significant with p value 0.108.

6. CORRELATION OF FAMILY HISTORY WITH ASTHMA

It was done by using Chi square test.

TABLE: 1 CHI SQUARE TEST FOR CORRELATION OF FAMILY HISTORY WITH BRONCHIAL ASTHMA

	Positive family history of asthma	**Negative family history of asthma**
Cases	**25**	**5**
Controls	**3**	**27**

- **Odds ratio = 25 x 27 / 3 x 5**

  = 45.

This shows that those with positive family history of bronchial asthma have 45 times more chance of getting asthma than those with negative family history of bronchial asthma.

7. CORRELATION OF FEV_1% AND PEFR WITH HRV PARAMETERS.

Correlation of FEV_1% and PEFR with HRV parameters was done by using Pearson correlation statistical analysis. r value < 0.05 was considered statistically significant.

Time domain measures

Mean RR, Mean HR, SDNN, RMSSD, NN50 counts and pNN50% had no significant correlation with both FEV_1% and PEFR.

Frequency domain measures

VLF, LF, LFnu, HFnu and LF/HF had no significant correlation with PEFR and FEV_1%.

HF had no significant correlation with PEFR.

HF showed significant negative correlation with FEV_1% with r value < 0.05. The decrease in FEV_1% increases HF.

TABLES AND CHARTS

TABLE: 2

COMPARISON OF AGE, WEIGHT, HEIGHT AND BMI OF BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS

Parameters	Group	Mean ± SD	p value
Age(yrs)	Controls	31.27 ± 7.08	0.706 NS
	Cases	32.03 ± 8.52	
Weight (kg)	Controls	62.4 ± 12.09	0.603 NS
	Cases	60.8 ± 11.62	
Height (cm)	Controls	161.53 ± 11.07	0.602 NS
	Cases	162.93 ± 9.56	
BMI (kg/m^2)	Controls	23.89 ± 2.85	0.282 NS
	Cases	23.05 ± 3.19	

NS - Not significant

TABLE: 3

COMPARISON OF PULSE AND B.P. OF BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS

Parameters	Group	Mean ± SD	p value
Pulse (bpm)	Controls	76.33 ± 7.26	0.523 NS
	Cases	75.27 ± 5.47	
Systolic B.P (mmHg)	Controls	120 ± 8.7	< 0.01 *
	Cases	112.33 ± 9.35	
Diastolic B.P (mmHg)	Controls	75 ± 9	0.354 NS
	Cases	73 ± 7.49	

NS- Not significant

* - Significant

TABLE: 4

COMPARISON OF FVC, FEV_1 AND FEV_1%OF BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS

Parameters	Group	Mean ± SD	p value
FVC (L)	Controls	3.65 ± 0.82	< 0.001 ***
	Cases	2.29 ± 0.70	
FEV_1 (L)	Controls	3.11 ± 0.69	< 0.001 ***
	Cases	1.56 ± 0.59	
FEV_1 %	Controls	84.82 ± 1.92	< 0.001 ***
	Cases	63.74 ± 7.9	

*** - Very highly significant

TABLE: 5

COMPARISON OF $FEV_{25-75\%}$ AND PEFR OF BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS

Parameters	Group	Mean ± SD	p value
$FEV_{25-75\%}$ (L)	Controls	3.43 ± 0.42	< 0.001 ***
	Cases	1.08 ± 0.5	
PEFR (L/sec)	Controls	7.69 ± 1.25	< 0.001 ***
	Cases	3.75 ± 1.79	

*** - Very highly significant

TABLE: 6

COMPARISON OF MEAN RR AND MEAN HR OF BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS

Parameters	Group	Mean ± SD	p value
MEAN RR	Controls	0.74 ± 0.1	< 0.05 *
	Cases	0.81 ± 0.13	
MEAN HR	Controls	83.23 ± 8.7	< 0.001 ***
	Cases	74.73 ± 6.97	

*** - Significant**

***** - Very highly significant**

TABLE: 7

COMPARISON OF SDNN, RMSSD, NN50 COUNTS AND pNN50% OF BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS

Parameters	Group	Mean ± SD	p value
SDNN (ms)	Controls	63.37 ± 27.75	< 0.001 ***
	Cases	37.30 ± 18.59	
RMSSD	Controls	51.98 ± 15.59	< 0.001 ***
	Cases	25.82 ± 9.33	
NN50 COUNTS	Controls	72.57 ± 9.96	< 0.01 **
	Cases	37.77 ± 6.05	
pNN50%	Controls	27.06 ± 3.16	< 0.001 ***
	Cases	12.90 ± 2.36	

** - Highly significant

*** - Very highly significant

TABLE: 8

COMPARISON OF VLF, LF AND HF OF BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS

Parameters	Group	Mean ± SD	p value
VLF (ms^2)	Controls	2334.23 ± 520.20	< 0.01 **
	Cases	1289.36 ± 285.89	
LF (ms^2)	Controls	331.07 ± 64.27	< 0.001 ***
	Cases	199.4 ± 35.27	
HF (ms^2)	Controls	85.9 ± 11.18	< 0.001 ***
	Cases	143.23 ± 25.46	

** - Highly significant

*** - Very highly significant

TABLE: 9

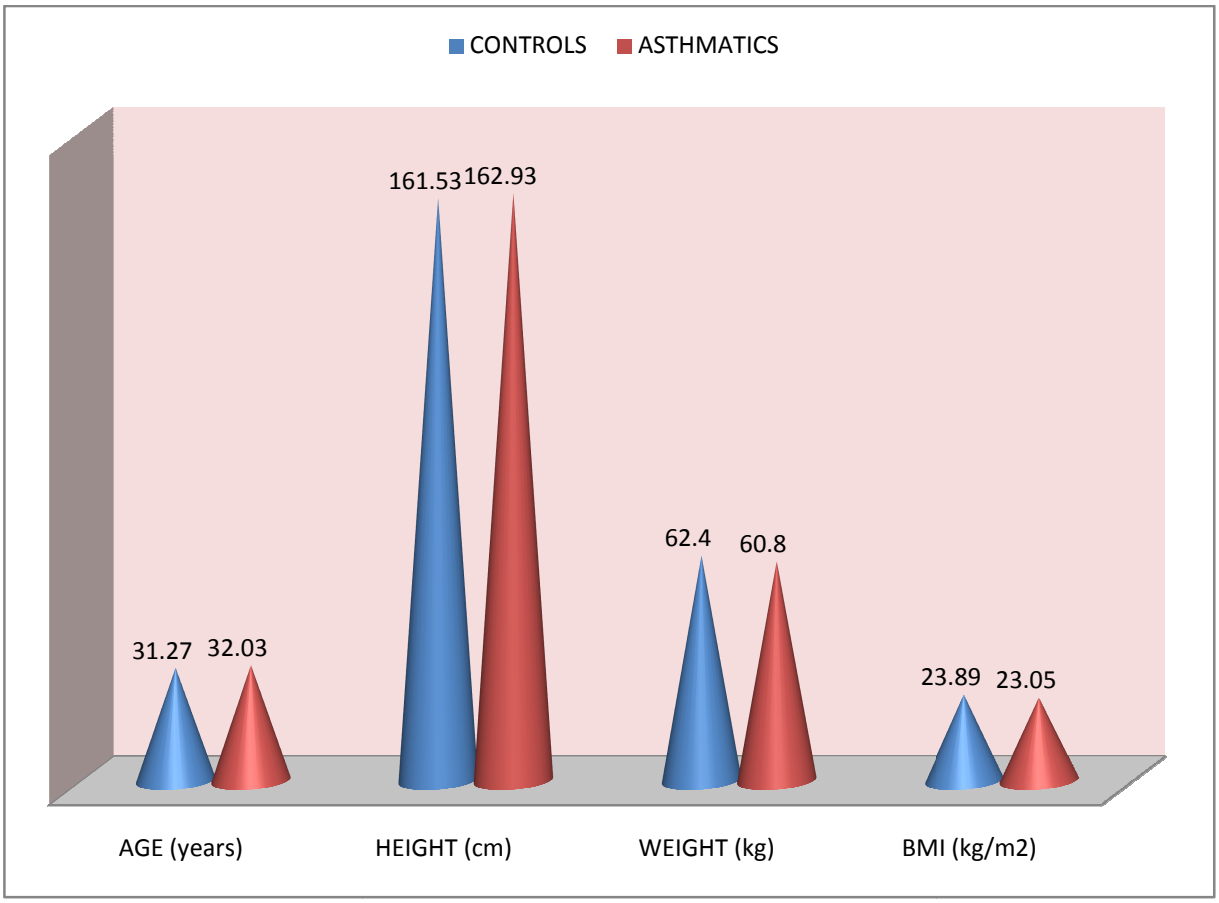
COMPARISON OF LF n.u, HF n.u AND LF/HF RATIO OF BRONCHIAL ASTHMA PATIENTS AND NORMAL SUBJECTS

Parameters	Group	Mean ± SD	p value
LF n.u	Controls	69.19 ± 9.72	0.236 NS
	Cases	68.89 ± 11.82	
HF n.u	Controls	30.78 ± 9.72	0.107 NS
	Cases	33.47 ± 15.79	
LF/HF ratio	Controls	3.85 ± 0.37	0.108 NS
	Cases	1.66 ± 0.24	

NS - Not significant

CHART: 1

COMPARISON OF BASELINE CHARACTERISTICS



p value for age is 0.706[NS]

p value for height is 0.603 [NS]

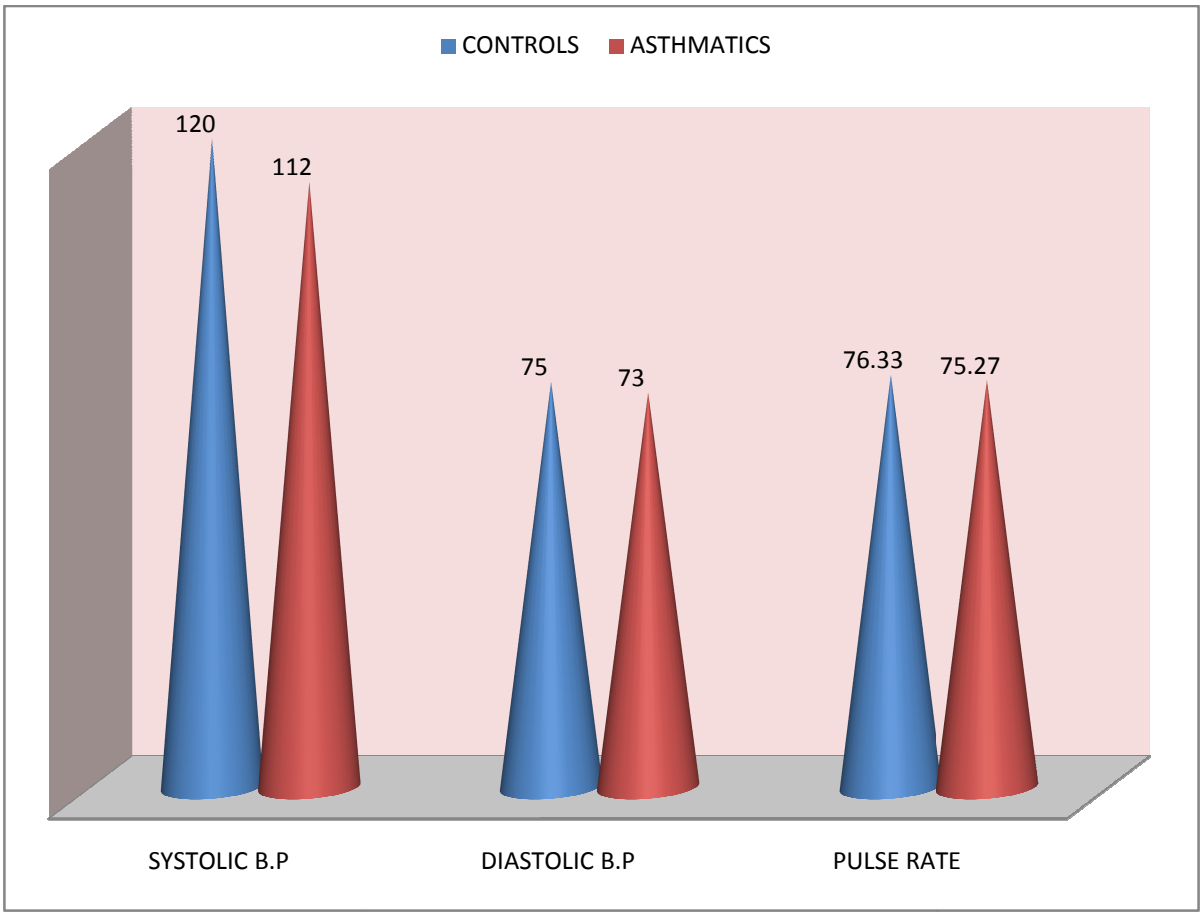
p value for weight is 0.602[NS]

p value for BMI is 0.282 [NS]

[NS] – Not significant.

CHART: 2

COMPARISON OF BLOOD PRESSURE AND PULSE



p value for SBP is < 0.01**

p value for DBP is 0.354 ^{NS}

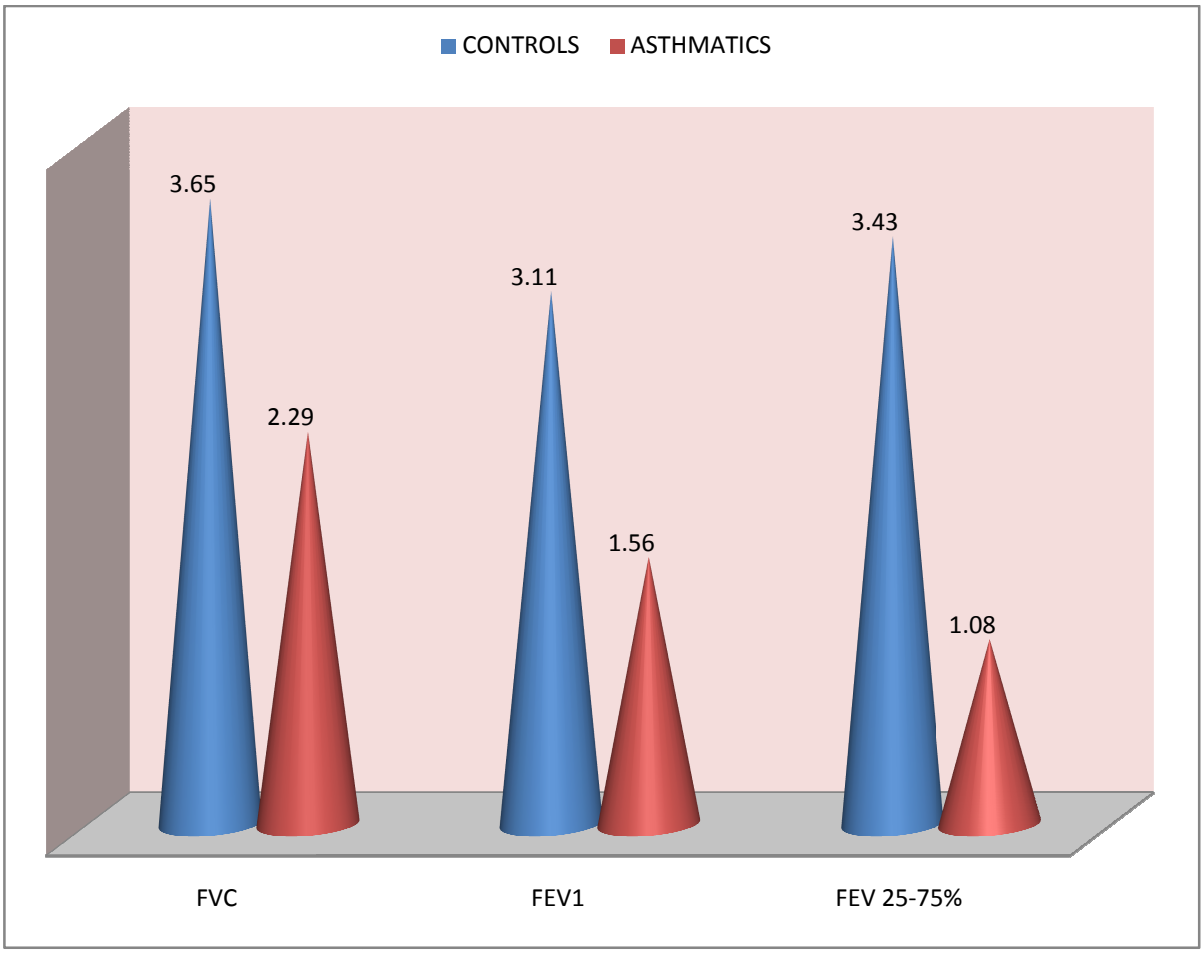
p value for pulse rate is 0.523^{NS}

** - Highly significant

^{NS} – Not significant

CHART: 3

COMPARISON OF FVC, FEV_1 AND $FEV_{25-75\%}$



p value for FVC is < 0.001***

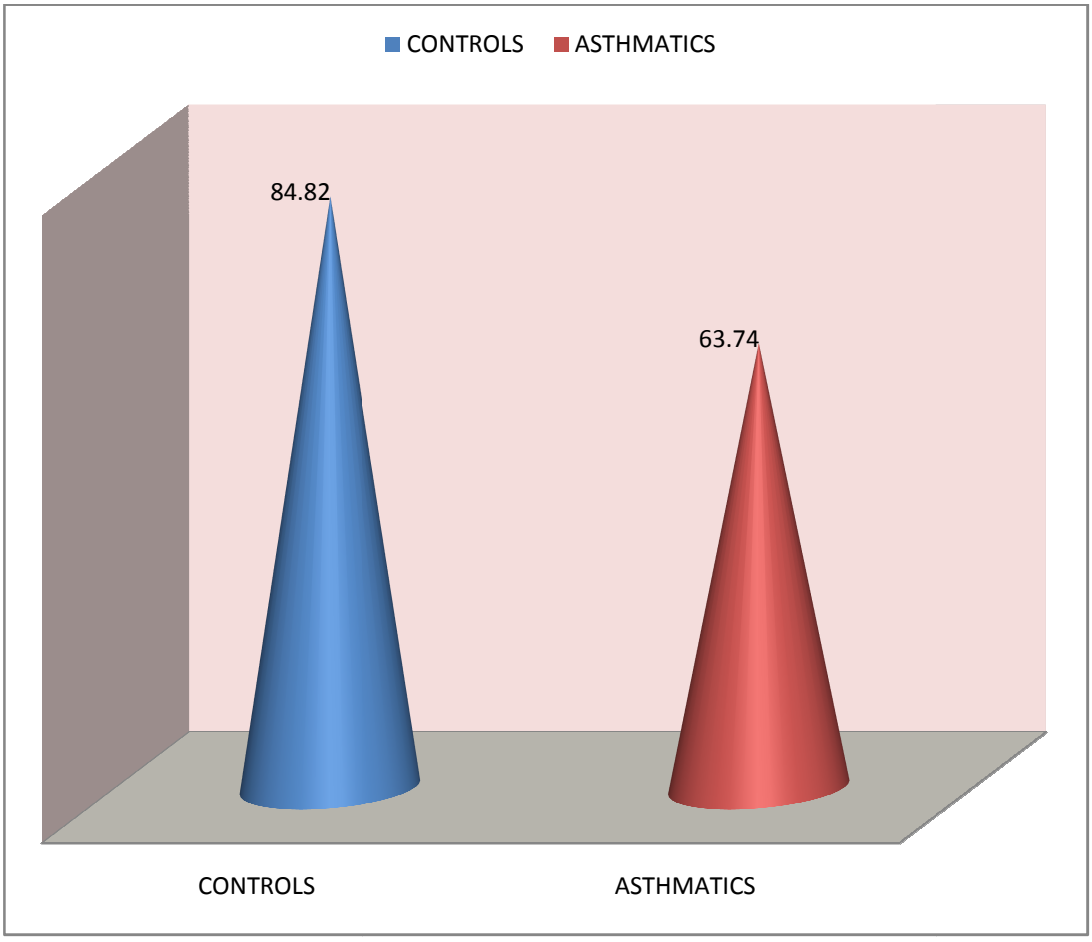
p value for FEV_1 is < 0.001***

p value for $FEV_{25-75\%}$ is < 0.001***

*** - Very highly significant

CHART: 4

COMPARISON OF FEV_1 %

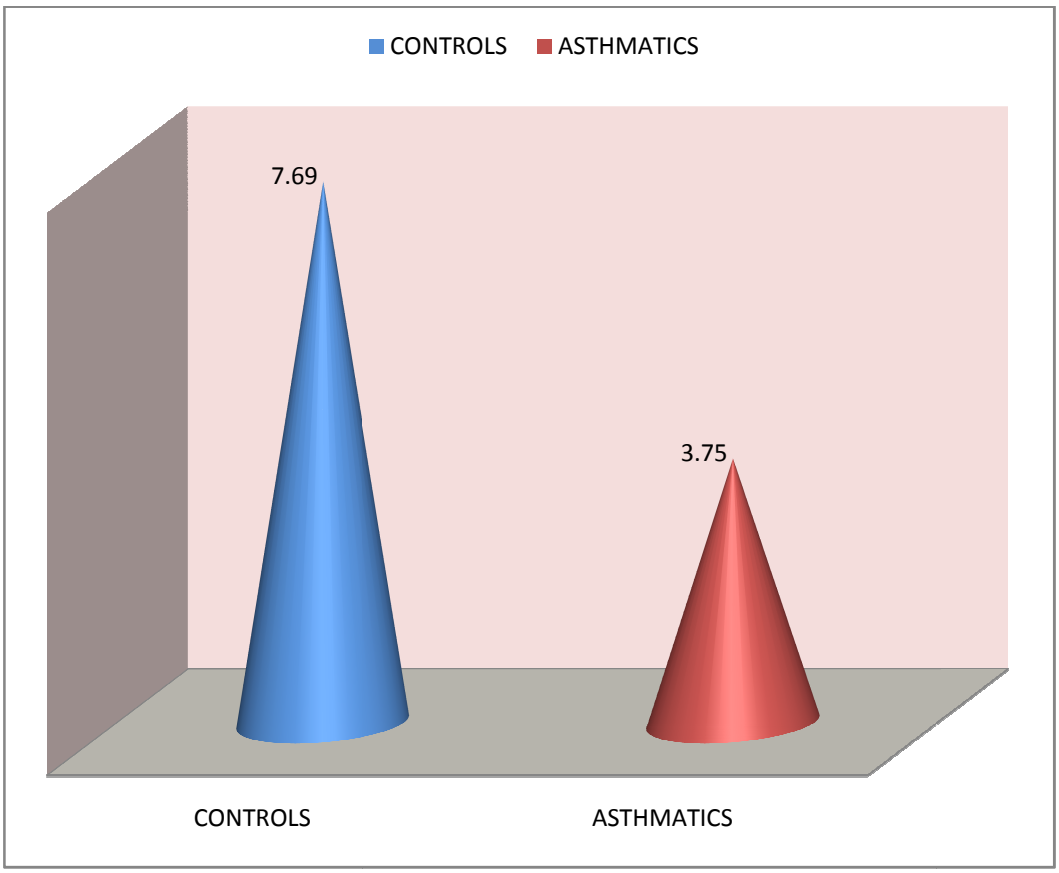


p value for FEV_1 % is < 0.001***

*** - Very highly significant

CHART: 5

COMPARISON OF PEFR

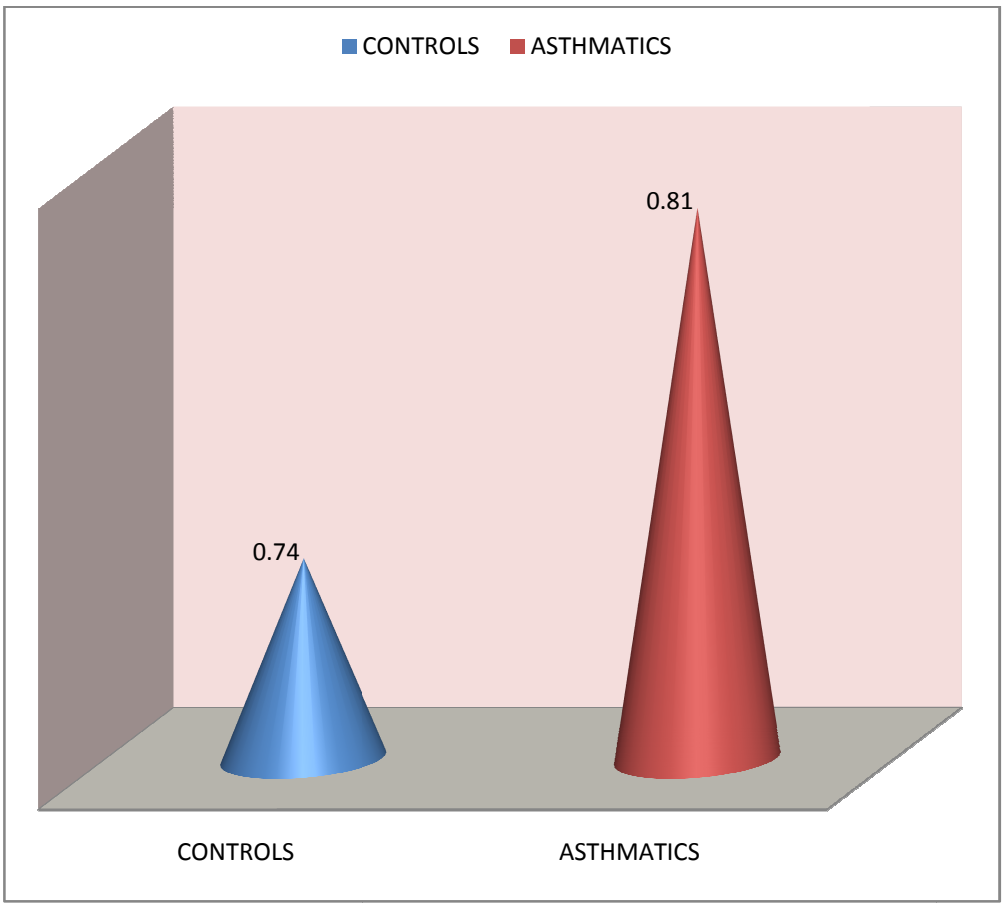


p value for PEFR is < 0.001***

*** - Very highly significant

CHART: 6

COMPARISON OF MEAN RR

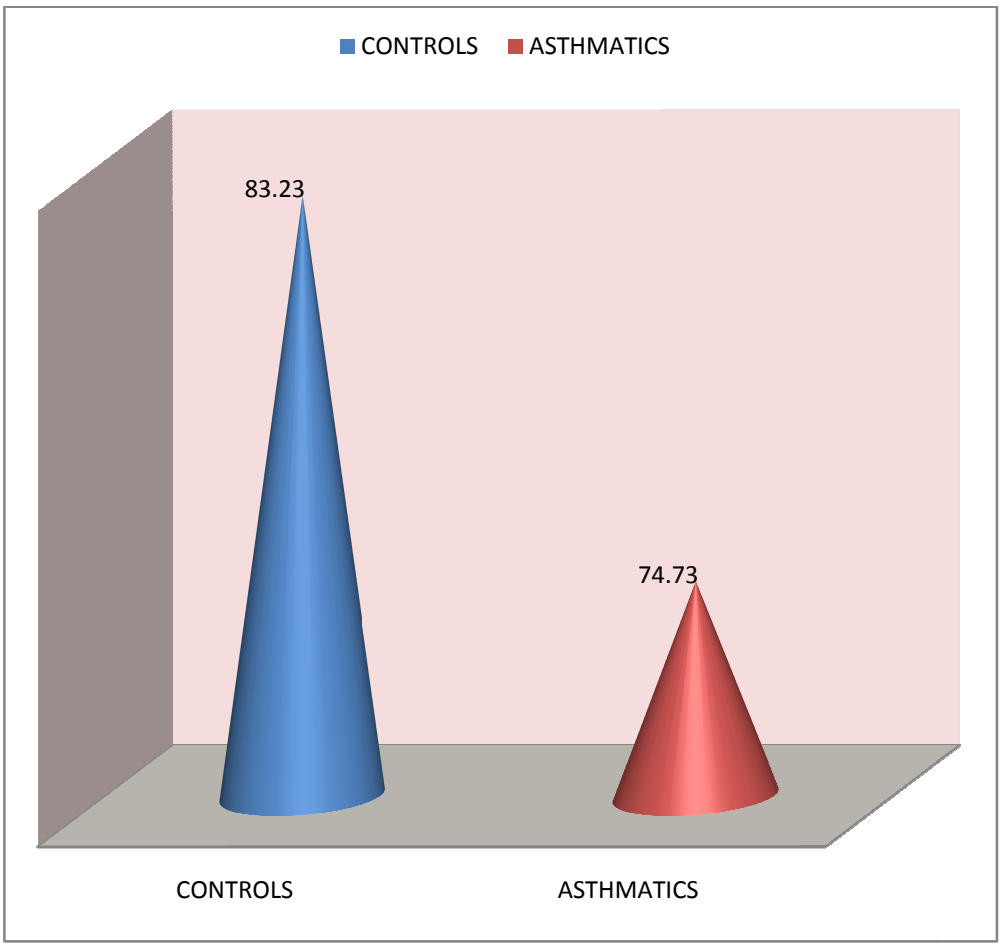


p value for Mean RR is < 0.05*

* - significant

CHART: 7

COMPARISON OF MEAN HR

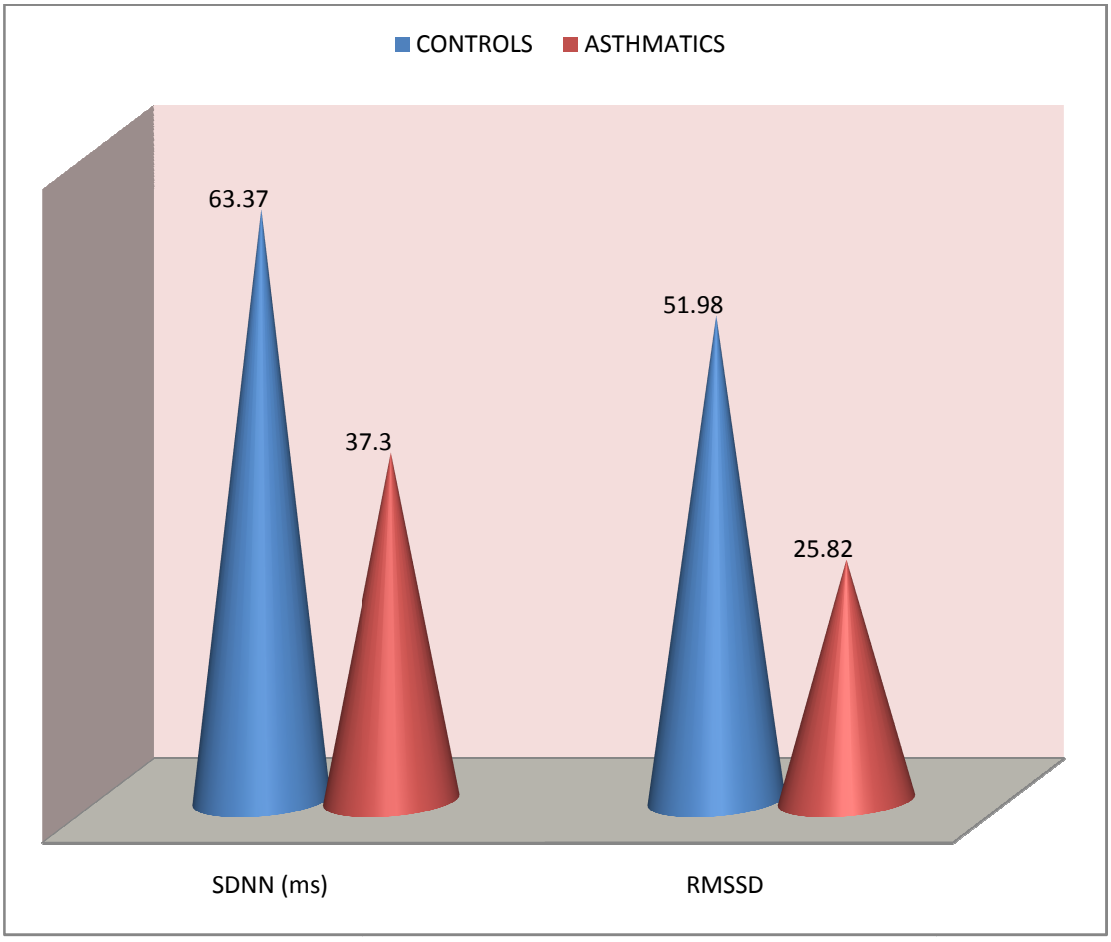


p value for Mean HR is < 0.001***

*** - Very highly significant

CHART: 8

COMPARISON OF SDNN AND RMSDD



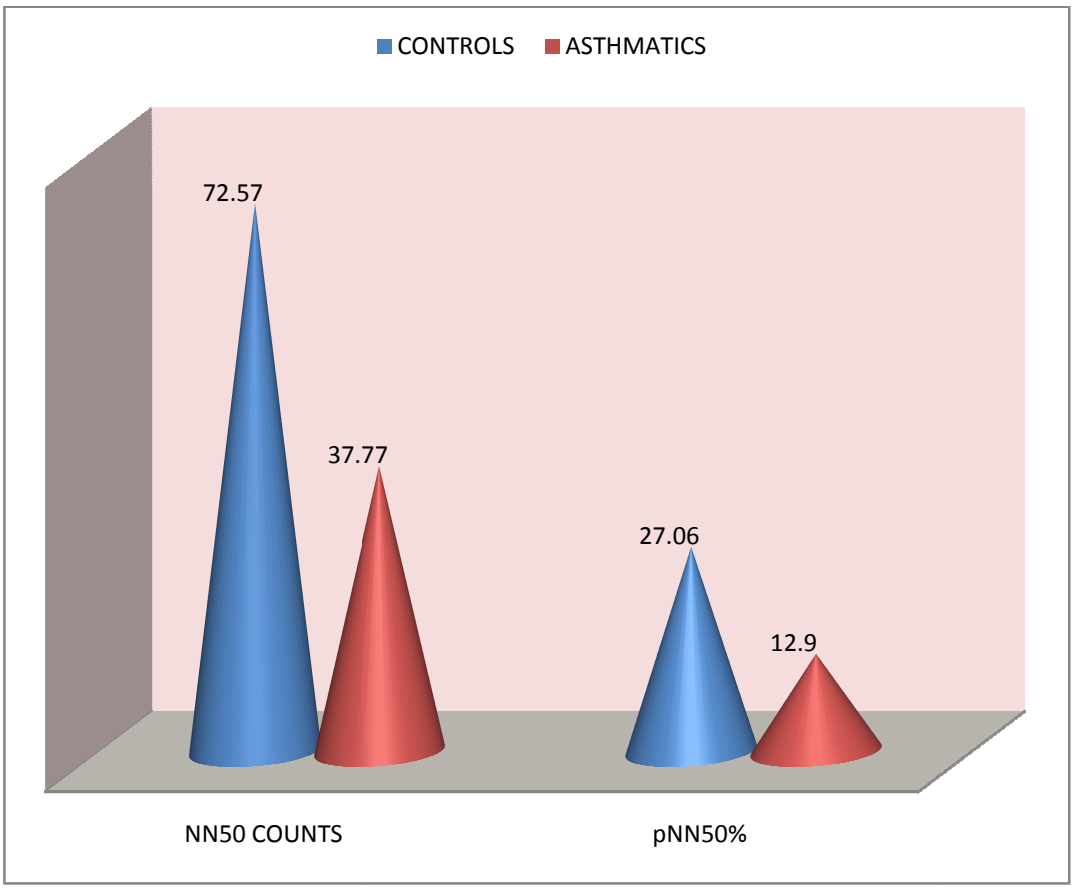
p value for SDNN is < 0.001***

p value for RMSSD is < 0.001***

*** - Very highly significant

CHART: 9

COMPARISON OF NN50 COUNTS AND pNN50%



p value for NN50 counts is < 0.01**

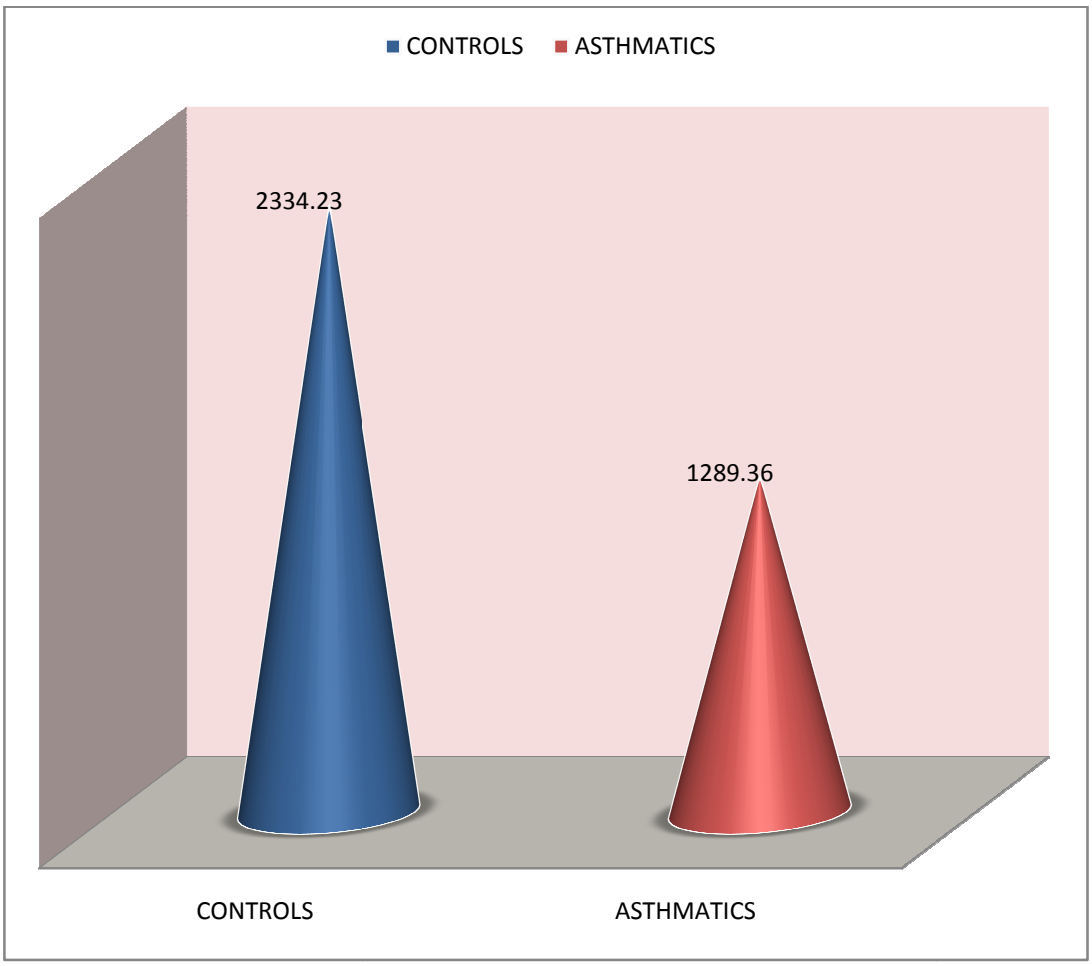
p value for pNN50% is < 0.001***

** - Highly significant

*** - Very highly significant

CHART: 10

COMPARISON OF VLF

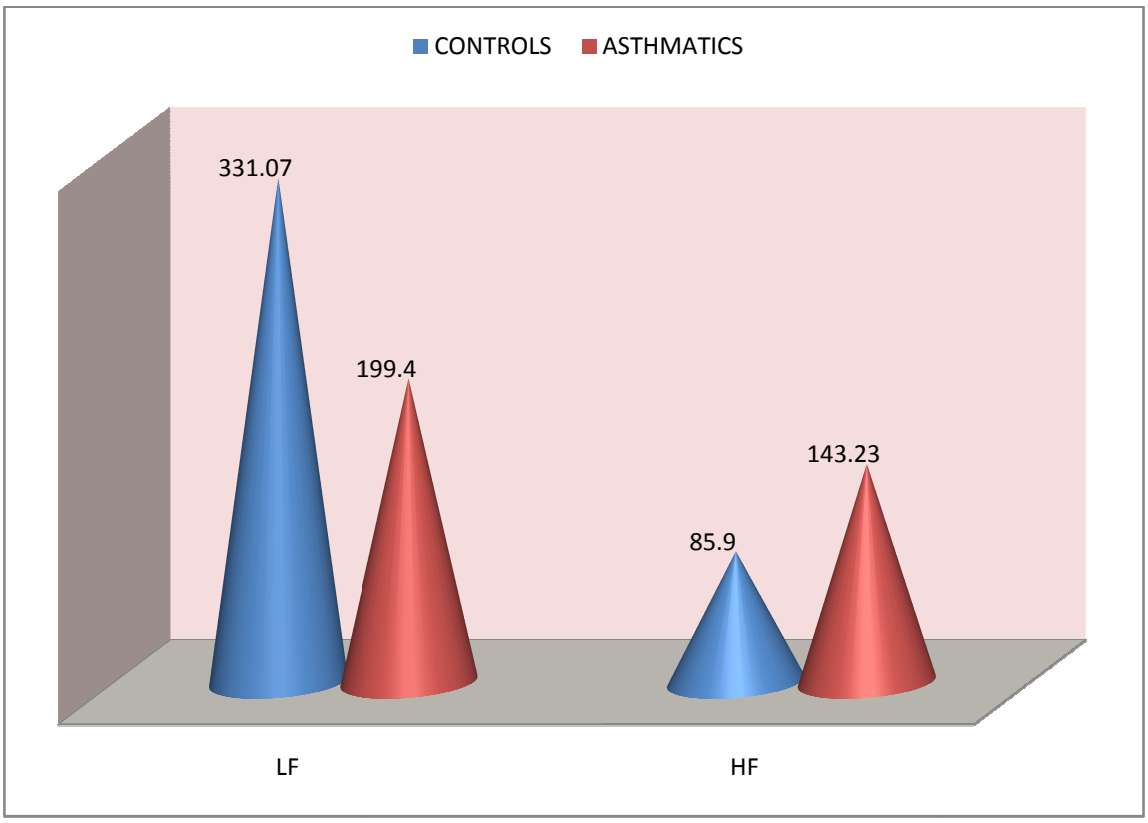


p value for VLF is < 0.01***

*** - Highly significant

CHART: 11

COMPARISON OF LF AND HF



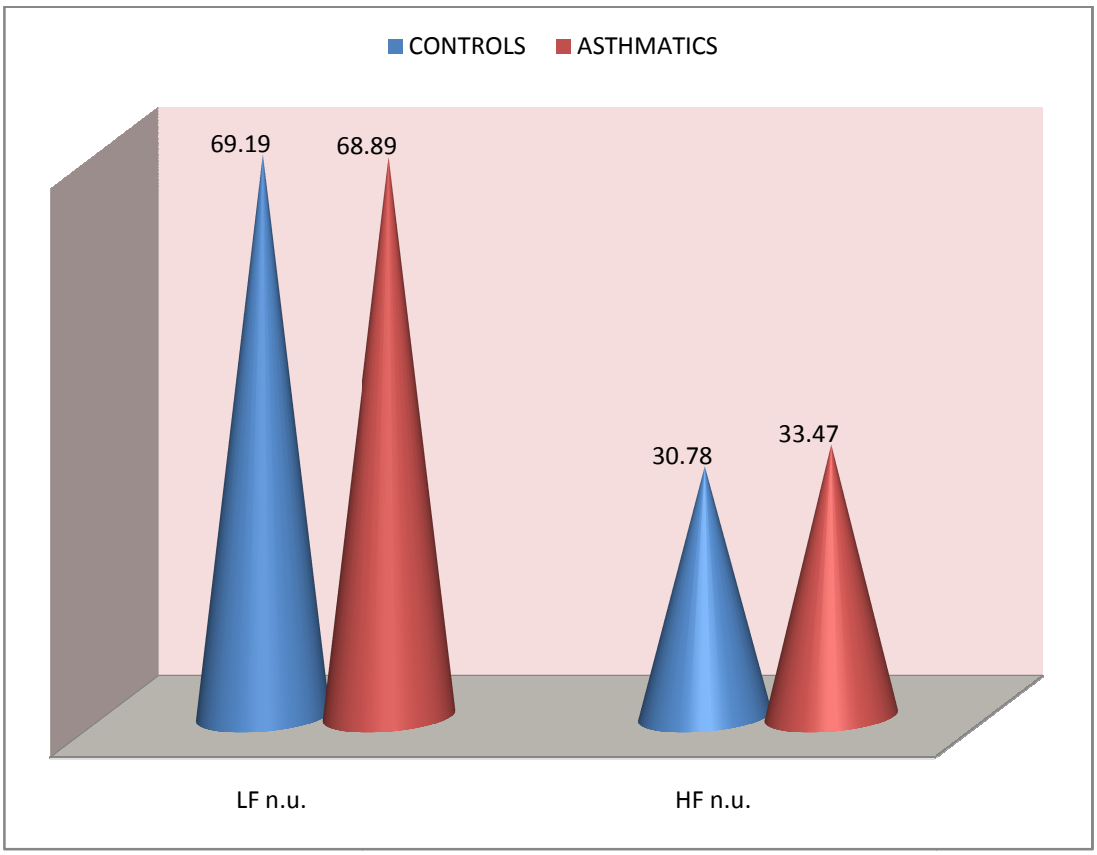
p value for LF is < 0.001***

p value for HF is < 0.001***

*** - Very highly significant

CHART: 12

COMPARISON OF LFnu AND HFnu



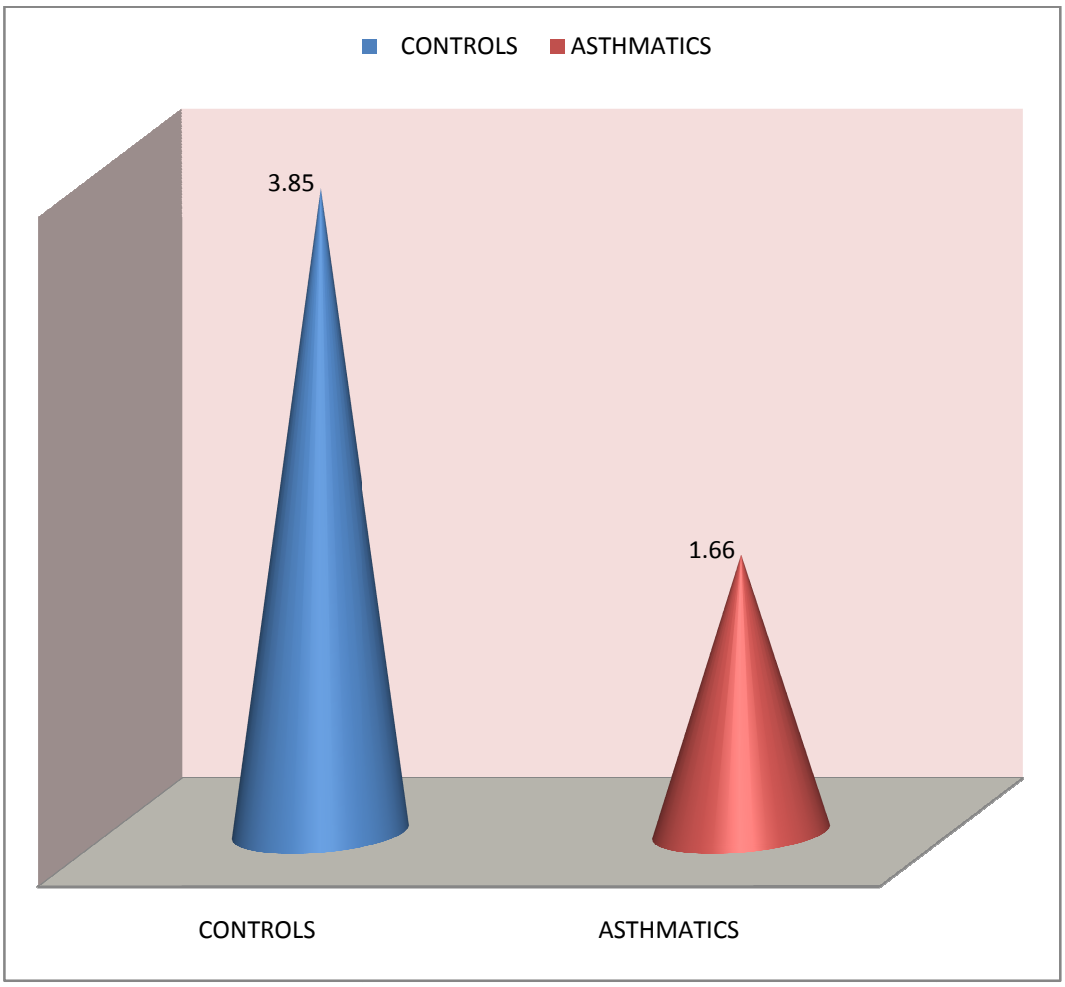
p value for LFnu is 0.236[NS]

p value for HFnu is 0.107 [NS]

[NS] – Not significant.

CHART: 13

COMPARISON OF LF/HF RATIO



p value for LF/HF ratio is 0.108 ^{NS}

^{NS} – Not significant.

DISCUSSION

DISCUSSION

Asthma is chronic inflammatory disorder of the airways, cells and cellular elements. Airway hyper responsiveness leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing.

Asthma constitutes 1% of the global disease burden. Annual worldwide mortality is 2,50,000. Mortality does not correlate with prevalence. Because modern clinical practice has revolutionized to find out and remove the exciting cause, allay the spasm during the paroxysm and to treat complications and sequelae.

The prevalence of bronchial asthma may vary within India because India is a country with dense population, changing climatic conditions, low socioeconomic and educational status, industrialization, traffic congestion and increasing number of automobiles, low health status and high prevalence of infections.

An obstructive pattern is seen in pulmonary function tests during asthma episodes. This includes a decrease in FEV_1 and FEV_1/FVC ratio due to increased resistance.

There is a reduction in forced vital capacity (FVC) because of hyperinflation of the lungs and increased residual volume. These patients breathe at such high lung volumes near the top of the pressure-volume curve, where lung compliance greatly decreases.

In order to treat any chronic illness, we need to follow guidelines that optimize its diagnosis and management. The Global Initiative for Asthma (GINA) committee reports are updated annually. Its guidelines and classifications are changing according to the needs. This could be due to the patient's awareness to visit the clinician or pulmonologists before it interrupts their daily activities.

Recent advances in pharmacotherapy also prevent the progression of disease to the next level. Most patients with positive family history present with mild symptoms progress to severe forms early in their life

within in a short period of time than others, due to genetic susceptibility. This study supports the findings of other similar studies.

Autonomic innervations are a primary control mechanism regulating HRV and cardiac performance. In normal persons the heart rate has a high degree of beat to beat variability and HRV changes with respiration, increases during inspiration and decreases during expiration[60].

HRV denotes the individual's autonomic tone and frequency domain measures are considered as best quantitative method for sympathetic and parasympathetic activity. A predominance of parasympathetic activity causes bradycardia and increase beat-to-beat variation, whereas increased sympathetic tone induces tachycardia and reduce beat-to-beat variations in HRV.

High beat-to-beat variation is desirable and lower beat-to-beat variation is an established predictor of cardiac mortality and morbidity.

Abnormal HRV predicts the cardiovascular etiology for mortality, coronary atherosclerotic development and cardiac arrhythmias.

The mean age, weight and height of the cases and the controls had showed no statistical significance. This suggests that the selection criterion of the control group was perfect.

The pulse of an individual is determined by the balance between sympathetic and parasympathetic activity. Decrease in pulse rate indicates more of parasympathetic activity and increase in pulse rate indicates more of sympathetic activity. In our study the pulse rate of the cases was decreased when compared to controls but was not statistically significant.

The systolic blood pressure depends on cardiac output which is the product of stroke volume and heart rate. Increase in sympathetic tone increases cardiac output and decrease in sympathetic tone decrease in cardiac output. In our study the systolic blood pressure of the cases was decreased when compared to that of the controls which was statistically significant. This fall in systolic blood pressure in cases could be attributed to decrease in sympathetic tone in cases.

The diastolic blood pressure depends on peripheral resistance. The tone of the blood vessels depends on the impulse transmission via peripheral sympathetic nerves to the blood vessels. The diastolic blood pressure in the cases was decreased when compared to control which was not statistically significant. This decrease in diastolic blood pressure could be attributed to decreased impulse transmission from vasomotor centre to blood vessels via peripheral sympathetic nerves.

Forced vital capacity is the maximum volume of air that is breathed out forcefully, rapidly and maximally. There was significant decrease in FVC of the cases compared to that of the controls. This is attributed to increased cholinergic stimulation which causes bronchoconstriction and air trapping causing increased residual volume.

FEV_1, FEV_1%, FEV_{25-75}% and PEFR were decreased in the cases compared to the controls due to bronchoconstriction as a result of increased cholinergic stimulation. Decreased FEV_{25-75} % suggest presence of small airway obstruction.

The mean R-R interval of the cases was significantly higher than that of the controls while the mean heart rate of the cases was significantly lower than that of the controls. This shows that there is increase in the parasympathetic tone compared to sympathetic tone. This was different from the study done previously by Garrard CS[59]. They observed increased sympathetic tone in asthmatics of longer duration.

SDNN, RMSSD, NN50 counts and pNN50% estimate high frequency variations in the heart rate. These parameters in the cases were significantly less compared to that of the controls. This suggests that high frequency variations in the heart rate were decreased in cases compared to the controls. High beat to beat variation is desirable and low beat to beat variation is a predictor of cardiac mortality and morbidity.

LF and LF nu denote sympathetically mediated HRV. LF was significantly reduced but the decrease of LF nu in cases was not statistically significant. This suggests that low frequency variation in the heart rate is less and sympathetic tone is decreased. This finding was similar to the studies done previously by Du J[51] and Gupta J[54].

HF and HF nu denote parasympathetically mediated HRV. HF was significantly increased in the cases while the increase of HF nu in cases was not statistically significant. This suggests that high frequency variation in the heart rate were more and parasympathetic tone was increased. This was similar to the studies done previously by Lutfi MF[47] and Gupta J[54].

LF/HF ratio of the cases was decreased than that of the controls but was not statistically significant. The LF/HF ratio measures sympathovagal balance and the primary cause for decreased LF/HF ratio in asthmatics was parasympathetic dominance than sympathetic dysfunction. This was similar to the study done by Gupta J[54].

90% (27 out of 30) of bronchial asthma patients had positive family history. Chi square test for correlation of family history with bronchial asthma showed an odds ratio of 45. This shows that bronchial asthma patients with positive family history have 45 times more chance of getting asthma than those with negative family history.

FEV_1% showed significant negative correlation with HF of frequency domain measures i.e., as FEV_1% decreases parasympathetic activity increases. This suggests that parasympathetic tone increases with the severity of the asthma.

CONCLUSION

CONCLUSION

- Spectral analysis of short term heart rate variability is a useful tool for quantifying ANS activities.

- In this study, we found out the autonomic dysfunctions in bronchial asthma by using spectral analysis of heart rate variability.

- Bronchial asthma initially affects parasympathetic nervous system and has a mild impact on sympathetic nervous system.

- Time domain measures of HRV showed significant parasympathetic dominance in asthmatics. The frequency domain measures also showed increased parasympathetic activity.

- Correlation of high frequency with FEV_1% by Pearson correlation statistical analysis showed negative correlation which means there was an increase in parasympathetic activity with increase in severity of asthma.

- To conclude, a significantly raised central vagal outflow and a concomitant low central sympathetic outflow is observed in asthmatics.

- This deranged sympathovagal balance with parasympathetic dominance could be the probable cause leading to airway obstruction in bronchial asthma.

- Low beat to beat variability was observed in asthmatics which is a predictor of cardiac mortality and morbidity.

- Most patients with bronchial asthma had positive family history. Since genetic susceptibility is a non modifiable factor, the environmental factors can be avoided.

- Identifying positive family history of asthma provides a basis for the preventive efforts to target the environmental risk factors.

- Unless prevented, asthmatic attacks can hinder day to day activities and cause significant reduction in quality of life.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Peter Crosta. et al. The asthma information section in Medical News Today, September 2007 and last updated on 5 March 2013.
2. Floyer JS. et al A treatise of the asthma. Divided into four parts printed for Richard Wilkin at St. Pauls' Churchyard, London. 1698.
3. World Health Organization: Asthma: updated May 2011.
4. Barbara p. yawn asthma management: are GINA guidelines appropriate for daily clinical practice? Respiratory Journal volume 14, issue 6, december 2005, pages 294–302.
5. Maddox L, Schwartz DA (2002). "The pathophysiology of asthma". Annu. Rev. Med. 53: 477–498.
6. Bateman ED, Hurd SS, Barnes PJ, et al, Global strategy for asthma management and prevention: GINA executive summary. European Respiratory Journal 2008. Jan; 31(1):143-178.
7. Liz Hunt et al asthma gene only active if inherited from mother'. The independent news paper article. 1992 august 15.
8. Burke W, Fesinmeyer M et al, Family history as a predictor of asthma risk. American Journal Preventive Medicine. 2003 Feb; 24(2):160-9.
9. Fernando Martinez et al, in CD14, Endotoxin, and Asthma Risk. American Thoracic Society. 2007 July; 4(3): 221–225.

10. Mathew A C1, Prince T G2, et al Prevalence and Risk Factors of Asthma in School going Children in South .Nepal Journal of Epidemiology 2012;2(1): 171-78
11. Moore WC, Pascual RM, et al "Update in asthma 2009". American Journal of Respiratory and Critical Care Medicine (June 2010). 181 (11): 1181–87.
12. M.R. Miller, J.Hankinson et al Standardisation of spirometry. European Respiratory Journal 2005; 26: 319–338
13. How to interpret spirometry results? Management of Chronic Obstructive Pulmonary Disease: Management of Adults in Primary and Secondary Care. London: NICE 28 October, 2011.
14. Cowen MK, Wakefield DB, Cloutier MM. Classifying asthma severity: objective versus subjective measures. J Asthma. 2007 Nov; 44(9):711–715.
15. Salpeter SR, Wall AJ, Buckley NS. Long-acting beta-agonists with and without inhaled corticosteroids and catastrophic asthma events. Am J Med. 2010 Apr; 123(4):322-8.e2.
16. Yale SH. Antonio Maria Valsalva (1666-1723). Clinical Medicine & Research 2005; 3:35-38.
17. Van der Velden VH, Hulsmann AR. et al, Autonomic innervation of human airways: structure, function, and pathophysiology in asthma. neuroimmunomodulation. 1999 May-Jun; 6(3):145-59.

18. Pal G K, Pravati Pal, Nivedita Nanda. Autonomic Nervous System: Functional Organization. Text book of Medical Physiology. 2nd edition, 2011, Ahuja publishing house: 201-208.
19. Donald Moss, PhD, Paul Lehrer, PhD, Richard Gevirtz, PhD,.Special issue: the emergent science and practice of heart rate variability biofeedback Association for Applied Psychophysiology & Biofeedback.2008 Nov; 36(1): 1-4.
20. Hon E. H., Lee S. T. (1965). Electronic evaluations of fetal heart rate patterns preceding fetal death, further observations. Am. J. Obset. Gynecol. 87, 814–826.
21. Honzikova N., Fisher B. (1978). Spectral analysis of resting variability of some circulatory parameters in man. Physiol. Bohemoslov. 27, 349–357.
22. Pagani M, Lombardi F, Malfatto et al. Power spectral analysis of heart rate and arterial pressure variability as a marker of sympatho-vagal interaction in man and in conscious dog. Circulation Research 1986; 59:178–193.
23. Bernardi L, Leuzzi S, Radaelli A et al. Low-frequency spontaneous fluctuations of R-R interval and blood pressure in conscious humans: a baroreceptor or central phenomenon? Clinical Sciences 1994; 87: 649–654.
24. Pomeranz B, Macaulay RJ, et al. Assessment of autonomic function in humans by heart rate spectral analysis. American Journal of Physiology 1985; 248:H151–H153.

25. Baselli G, Cerutti S, Civardi S,et al. Heart rate variability signal processing: a quantitative approach as an aid to diagnosis in cardiovascular pathologies. International Journal of Biomedicine and Computers 1987; 20:51–70.
26. Hall, Respiratory insufficiency - Pathophysiology, diagnosis, oxygen therapy. Guyton and Hall Textbook of Medical Physiology. Elsevier Publishers. 12th edition, 2012: 515-523.
27. Stephane Jorge, Samuel Delerme, et al, Cardiac asthma in elderly patients: incidence, clinical presentation and outcome. Cardiovascular Disorders. 2007May; 7: 16.
28. Swartz, J., Scheynius, A., et al. Allergic disease and sensitization in Steiner school children. The Journal of Allergy and Clinical Immunology. 2006; 117(1), 59-66.
29. Zhang WP., et al, effect of acupuncture on the pulmonary function and heart rate variability in different state of asthma.2007 Feb; 32(1):42-48.
30. Indukurana. Autonomic Nervous System. Text Book of Physiology. 1st edition. 995-997.
31. Pal G K, Pravati Pal, Nivedita Nanda. Control of Autonomic functions; Autonomic dysfunctions. Text book of Medical Physiology. 2nd edition, 2011, Ahuja publishing house: 217-226.

32. Kim E. Barret, Susan M. Barman, et al., Autonomic Nervous System. Ganong's Review of Medical Physiology. Tata McGraw Hill Publishers. 24th edition, 2012: 255-267.

33. Hypothalamus and autonomic nervous system: O.U.C.H LINKS Washington School of Medicine; Neuroscience Tutorial, 1997.

34. Paul L.Enright, Beverly J.Ward, et al., Asthma and Its Association with Cardiovascular Disease in the Elderly. Journal of Asthma.1996; 33(1):45-53.

35. Michela Bellocchia et al., Predictors of cardiovascular disease in asthma and chronic obstructive pulmonary disease. Multidisciplinary Respiratory Medicine.2013, 8:58

36. Carlos Iribarren C, Tolstykh IV, Eisner MD. Are patients with asthma at increased risk of coronary heart disease? Int J Epidemiol. 2004; 33(4):743–748.

37. Eckert, M. A short history of spirometry and lung function tests. 2004. Available at: http://medizin.li/spirometer/spirometer-history.html. Accessed April 14, 2004.

38. Sprigge, J.S. Sir Humphry Davy; his researches in respiratory physiology and his debt to Antoine Lavoisier. Anaesthesia. 2002; 57(4): 357-359.

39. Cleeland, J., Burt, S. Charles Turner Thackrah: a pioneer in the field of occupational health. Occup Med (Lond). 1995 Dec; 45(6):285-97.

40. Petty, T.L. John Hutchinson mysterious machine revisited. Chest. 2002; 121: 219-224.

41. Bassett, D., Howley, E., Thompson, D., King, G., Strath, S., McLaughlin, J., Parr, B. Validity of inspiratory and expiratory methods of measuring gas exchange with a computerized system. Journal of Applied Physiology. 2001; 91: 218 - 224.

42. Ewing DJ, Martin CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests. Diabetes Care. 1985;8: 491-492.

43. Wolf MM, Hunt D, Varigos CA, Sloman JG. Sinus arrhythmia in acute myocardial infarction. Med J Aust. 1978; 2: 52-53.

44. Akselrod S, Ubel FA, Gordon D, Barger AC, Shannon DC. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat to beat cardiovascular control. Science. 1981; 213: 220-222.

45. Kazuma N[1], Otsuka K, Miyakawa M, Shirase E, Matsuoka I, Murata M Seasonal variation in heart rate variability in asthmatic children. Chronobiol Int. 2000 Jul; 17(4):503-11.

46. Domnik NJ[1], Seaborn G, Vincent SG, Akl SG, Redfearn DP, Fisher JT, OVA-induced airway hyperresponsiveness alters murine HRV and body temperature. Front Physiology. 2012 Dec 4; 3:456.

47. Mohamed F. Lutfi**,** Autonomic modulations in patients with bronchial asthma based on short-term heart rate variability Lung India. 2012 Jul-Sep; 29(3): 254–258.

48. Sekerel BE[1], Sahiner UM, Can M, Abali G, Alehan D, Aytemir K, The effects of inhaled formoterol on the autonomic nervous system in adolescents with asthma. Ann Allergy Asthma Immunol. 2011 Sep; 107(3):266-72.

49. Tsai YS, Lai FC, Chen SR, Jeng C. The influence of physical activity level on HRV among asthmatic adults. J Clin Nurs. 2011 Jan; 20(1-2):111-8.

50. Campbell TS, Lavoie KL, Bacon SL, Scharf D, Aboussafy D, Ditto B. Asthma self-efficacy, high frequency HRV, and airflow obstruction during negative effect in daily life. Int J Psychophysiol. 2006 Oct; 62(1):109-14.

51. Du J, He J, Wang Y. A study of HRV in asthma.Article in Chinese2001 Dec; 24(12):744-5.

52. Korematsu S. Autoregressive analysis of HRV and BP in asthmatic children and difference of severity. Article in Japanese. 1995 Sep; 44(9):1140-1149.

53. Mitsunori Murata, Norio Kazuma, Kuniaki Otsuka, Ikumi Matsuoka, Heart Rate Variability During 24 Hours in Asthmatic Children 1997, Vol. 14, No. 6, Pages 597-606.

54. Gupta J, Dube A, Singh V, Gupta RC. Spectral analysis of heart rate variability in bronchial asthma patients. Indian J Physiol Pharmacol. 2012 Oct-Dec; 56(4):330-6.

55. Gomes EL, Sampaio LM, Costa IP, Dias FD, Ferneda VS, Silva GA, Costa D. Analysis of autonomic modulation during maximal and submaximal work rate and functional capacity in asthmatic children. 2013 Aug; 50(6):613-8.

56. Emin O, Esra G, Aysegul D, Ufuk E, Ayhan S, Rusen DM. Autonomic nervous system dysfunction and their relationship with disease severity in children with atopic asthma. Respir Physiol Neurobiol. 2012 Sep 30; 183(3):206-10.

57. Ostrowska-Nawarycz L, Wronski W, Blaszczyk J, Buczylko K, Nawarycz T. The heart rate variability analysis in youth and children with bronchial asthma. Pol Merkur Lekarski. 2006 Apr; 20(118):399-403.

58. Jartti TT, Tahvanainen KU, Kaila TJ, Kuusela TA, Koivikko AS, Vanto TT. Cardiovascular autonomic regulation in asthmatic children evidenced by spectral analysis of heart rate and blood pressure variability. Scand J Clin Lab Invest. 1996 Oct; 56(6):545-54.

59. Garrard CS, Seidler A, McKibben A, McAlpine LE, Gordon D. Spectral analysis of heart rate variability in bronchial asthma. Clin Auton Res. 1992 Apr; 2(2):105-11.

60. Task force of the European society of cardiology and the North American society of pacing and electrophysiology, Heart rate variability: standard of measurement, physiological interpretation and clinical use. Circulation 1996; 93: 1043-1065.

ANNEXURE

A STUDY OF AUTONOMIC MODULATIONS WITH SHORT TERM HEART RATE VARIABILITY IN BRONCHIAL ASTHMA PATIENTS AND ITS CORRELATION WITH PULMONARY FUNCTION TESTS

PROFORMA

Name:

Age:

Sex:

IP /OP Number:

Occupation:

Address:

HISTORY REGARDING THE CASE

Duration of Illness

PAST HISTORY

Hypertension

Diabetes

Any Other illness

PERSONAL HISTORY

Food Habits:

Exercise :

Smoking :

Alcohol :

Tobacco Chewing:

FAMILY HISTORY

Any Similar Problems:

DRUG HISTORY

Details of asthma treatment:

Details of any other drug intake:

EXAMINATION OF THE PATIENT:

GENERAL EXAMINATION

Nutrition

Build

Clubbing

Cyanosis

Jaundice

Anemia

Pulse rate

Resting BP

SYSTEMIC EXAMINATION:

Examination of CVS

Examination of RS

Examination of ABDOMEN

Examination of CNS

INVESTIGATIONS:

Pulmonary Function Test

ANTHROPOMETRIC MEASUREMENTS

HEIGHT in cms

WEIGHT in kgs

HEART RATE VARIABILITY

FREQUENCY DOMAIN MEASURES:

LF POWER

HF POWER

LF/HF RATIO

LF nu

HF nu

TIME DOMAIN MEASURES

Mean RR

Mean HR

SDNN

RMSSD

NN50

PNN50

CONSENT FORM

A study of autonomic modulations with short term heart rate variability in bronchial asthma patients and its correlation with pulmonary function tests

MD Thesis research project

Department Of physiology

PSG IMS &R.

I,…….. have been explained about the purpose of the research study on HRV analysis. I have received verbal information on the above study and on the possible benefits and discomforts of ECG recording. I have been given chance to discuss the study and ask questions.

By signing this form, I give my consent to take part in this study and I am aware that my participation is entirely voluntary. I agree that my personal data including data relating to my physical or mental health may be used for this study. I have been assured that the information from this study, if published in scientific journals or presented at scientific meetings, will not reveal my identity.

Truly,

……

(Subject name, signature)

WITNESS:

DATE AND TIME:

ASTHMATICS DATA SHEET

S.NO	AGE years	HEIGHT cm	WEIGHT kg	BMI Kg/m^2	FVC L	FEV_1 L	FEV_1% %	$FEV_{25-75\%}$ L/sec	PEFR L/sec	PULSE bpm	SBP mmHg	DBP mmHg
1	28	165	63	23.1	1.6	0.89	55.6	0.46	1.58	72	110	70
2	20	150	46	20.4	2.56	1.8	70.3	1.3	3.8	74	120	70
3	43	167	71	25.5	2.63	1.81	69.5	1.27	4.16	78	100	60
4	45	175	80	26.1	2.29	1.53	64.7	0.85	3.93	78	100	70
5	38	169	74	25.9	2.43	1.62	65.7	1.01	4.37	80	120	80
6	35	151	51	22.4	1.84	1.4	76	1.15	3.31	76	110	70
7	41	157	53	21.5	1.91	1.48	65	1.3	2.81	68	130	80
8	24	166	73	26.5	2.9	2.17	73.5	1.62	6.5	88	120	80
9	20	150	41	18.2	1.26	0.78	59.4	0.68	1.74	84	120	80
10	20	176	66	21.3	3.3	2.19	66.1	1.26	5.59	76	110	70
11	33	163	57	21.5	2.24	1.16	51.9	0.54	3.15	68	110	70
12	43	171	51	17.4	2.03	0.87	43.3	0.47	1.66	66	120	80
13	37	156	60	24.7	1.63	0.91	56	0.47	1.46	70	110	60
14	45	167	89	31.9	2.53	1.89	64.4	1.45	5.35	72	100	60
15	22	155	50	20.8	2.25	1.77	67.9	1.57	3.92	74	110	80

S.NO	AGE years	HEIGHT cms	WEIGHT kg	BMI Kg/m^2	FVC L	FEV_1 L	FEV_1% %	$FEV_{25-75\%}$ L/sec	PEFR L/sec	PULSE bpm	SBP mmHg	DBP mmHg
16	28	156	56	23	1.5	1.14	67	0.99	1.76	78	120	80
17	45	153	63	26.9	1.6	1.24	64.3	0.95	3.6	82	110	70
18	38	175	71	23.2	2.89	1.78	61.1	0.89	5.3	80	100	70
19	31	165	62	22.8	2.9	2.35	66.6	1.71	5.62	84	100	60
20	29	176	67	21.6	4.13	2.83	68.4	1.86	6.32	68	110	70
21	24	162	54	20.6	2.6	1.78	71.5	1.3	4.28	68	110	70
22	20	174	47	18.5	2.16	1.08	49.3	0.56	2.34	72	110	80
23	37	149	49	22.1	1.34	0.86	69.3	0.58	2.41	70	100	70
24	29	150	57	25.3	1.2	0.67	55.8	0.32	1.33	74	120	80
25	39	155	63	26.2	2.1	1.24	58.6	0.65	2.92	74	120	70
26	31	160	62	24.2	2.15	1.13	52.5	0.56	1.79	72	110	70
27	40	157	67	27.2	2.33	1.78	65.2	1.47	3.96	78	110	70
28	27	183	78	23.3	3.75	2.86	73.7	2.01	8.65	76	130	80
29	29	162	41	18.6	1.79	1.33	72.7	0.96	3.22	78	130	90
30	20	173	62	20.7	2.96	2.33	67	2.08	5.88	80	100	80

S.NO	FAMILY H/O	Mean RR	Mean HR	SDNN ms	RMSSD ms	NN50 counts	pNN50 %	VLF ms^2	LF ms^2	HF ms^2	LF/HF	LF nu	HF nu
1	YES	0.627	96	29.308	14.565	6	1.3	60	198	481	1.75	66.3	33.7
2	YES	0.64	94	38.527	26.975	28	6.5	260	195	375	3.4	79.4	20.6
3	YES	0.756	79	32.37	38.887	24	25.3	493	178	84	1.83	66.7	33.3
4	NO	0.752	80	93.4	39.971	58	47.5	1757	236	115	1.6	64	36
5	YES	0.69	87	30.76	19.301	7	1.7	326	131	4	3.75	84.4	15.2
6	YES	0.854	70	24.608	24.202	6	1.7	992	98	178	1.52	65.2	35.3
7	YES	0.705	85	16.787	13.041	10	2.1	1879	263	22	1.72	64.5	35.3
8	YES	0.697	86	47.23	39.034	24	25	2536	52	79	2.93	77	23
9	YES	0.77	78	39.696	26.629	20	4.7	360	120	95	4.65	84.8	15.2
10	YES	0.813	74	87.922	29.509	87	35.1	6687	1006	238	1.15	54.7	45.3
11	NO	0.717	84	38.419	34.35	71	14.2	45	158	39	3.43	78.3	21.7
12	YES	0.792	76	24.3	20.815	2	0.5	1045	182	112	2.35	73	27
13	YES	0.864	82	38.701	20.075	75	21.6	2985	171	48	3.02	76.6	24
14	YES	0.711	84	30.62	30.42	37	8.9	367	178	29	1.86	66.4	33.6
15	YES	0.831	72	65.502	36.871	126	40.8	663	227	112	3.54	81.6	90.2

S.NO	FAMILY H/O	Mean RR	Mean HR	SDNN ms	RMSSD ms	NN50 counts	pNN50 %	VLF ms^2	LF ms^2	HF ms^2	LF/HF	LF nu	HF nu
16	NO	0.846	71	44.179	35.171	48	13.5	3503	403	87	0.63	50	50
17	YES	0.888	88	51.06	22.083	102	30.5	2186	215	59	1.16	55.9	44.1
18	YES	0.849	71	42.219	34.446	49	13.9	2483	192	26	2.84	77.5	22.7
19	YES	0.831	72	34.742	33.454	50	13.6	920	143	37	1.81	38.1	61.9
20	YES	0.696	86	23.15	21.672	13	2.9	91	71	95	3.15	78.4	21.6
21	YES	0.618	97	33.756	15.283	1	0.2	60	36	413	2.43	74.7	25.3
22	YES	0.564	96	18.833	12.858	20	4.3	29	33	7	1.71	80.5	19.3
23	NO	0.778	77	29.209	27.511	29	7.3	900	156	317	2.91	76.9	23.1
24	YES	0.57	95	11.342	21.551	40	11.9	15	38	252	2.35	72.7	27.3
25	YES	0.773	78	36.687	35.714	77	19.4	841	168	107	2.57	74	26
26	YES	0.581	93	20.929	9.546	30	6.9	22	29	314	2.5	76.3	22.5
27	YES	0.802	75	48.148	18.767	2	0.6	2551	356	51	0.74	46.6	53.4
28	NO	0.7	86	21.917	21.04	14	3.2	254	135	27	1.25	57.3	42.4
29	YES	0.562	97	21.15	11.913	2	0.4	19	30	422	2.06	69.6	30.4
30	YES	0.888	88	43.712	38.995	75	21.7	4352	584	72	1.16	55.4	44.6

CONTROLS DATA SHEET												
S.NO	**AGE years**	**HEIGHT cm**	**WEIGHT kg**	**BMI Kg/m^2**	**FVC L**	**FEV_1 L**	**FEV_1% %**	**$FEV_{25-75\%}$ L/sec**	**PEFR L/sec**	**PULSE bpm**	**SBP mmHg**	**DBP mmHg**
1.	**20**	**160**	**55**	**21.5**	**3.93**	**3.47**	**84.3**	**3.01**	**7.83**	**74**	**120**	**80**
2.	**20**	**154**	**50**	**21.08**	**3.9**	**3.46**	**84.83**	**3.6**	**7.48**	**72**	**120**	**70**
3.	**37**	**152**	**61**	**26.4**	**3.41**	**3.08**	**86.31**	**3.6**	**5.86**	**70**	**130**	**80**
4.	**42**	**160**	**72**	**28.1**	**3.9**	**3.48**	**85.52**	**3.86**	**7.26**	**78**	**110**	**70**
5.	**29**	**175**	**66**	**21.6**	**4.8**	**4.04**	**86.24**	**3.82**	**9.81**	**76**	**130**	**80**
6.	**31**	**170**	**69**	**23.88**	**4.48**	**3.85**	**85.94**	**4.19**	**8.04**	**80**	**130**	**80**
7.	**43**	**180**	**81**	**25**	**4.15**	**3.61**	**82.86**	**3.51**	**8.2**	**84**	**130**	**90**
8.	**31**	**167**	**57**	**20.5**	**4.57**	**3.67**	**80.31**	**3.35**	**8.69**	**62**	**110**	**60**
9.	**25**	**172**	**83**	**28.1**	**4.94**	**4.21**	**85.22**	**3.9**	**8.12**	**76**	**120**	**70**
10.	**28**	**157**	**54**	**25.96**	**3.34**	**2.8**	**83.78**	**3.31**	**7.43**	**74**	**110**	**70**
11.	**32**	**152**	**58**	**25.2**	**2.56**	**2.24**	**87.5**	**2.88**	**7.2**	**82**	**120**	**70**
12.	**33**	**160**	**65**	**25.4**	**4.02**	**3.43**	**85.32**	**3.38**	**7.56**	**76**	**120**	**80**
13.	**26**	**182**	**70**	**21.2**	**4.17**	**3.42**	**83.01**	**3.51**	**9.68**	**76**	**120**	**80**
14.	**32**	**175**	**88**	**28.7**	**4.85**	**3.99**	**82.27**	**3.79**	**9**	**80**	**130**	**80**
15.	**25**	**160**	**50**	**19.5**	**3.24**	**2.81**	**86.73**	**3.19**	**6.34**	**66**	**120**	**70**

S.NO	AGE years	HEIGHT cm	WEIGHT kg	BMI Kg/m^2	FVC L	FEV_1 L	FEV_1% %	$FEV_{25-75\%}$ L/sec	PEFR L/sec	PULSE bpm	SBP mmHg	DBP mmHg
16.	24	147	46	21.3	3.02	2.61	87.04	2.89	6.1	84	130	90
17.	36	144	45	21.7	2.74	2.31	84.31	2.9	7.46	80	130	80
18.	34	170	80	27.7	3.66	3.11	84.97	3.84	9.18	84	110	60
19.	42	165	70	25.7	3.62	3.02	82.31	3.62	7.62	90	110	70
20.	38	154	56	23.6	2.82	2.34	82.98	3.27	6.45	76	120	80
21.	32	154	67	28.5	2.83	2.4	84.81	3.26	7.46	74	130	90
22.	21	175	66	21.3	4.53	3.84	84.77	3.87	8.75	84	120	70
23.	23	170	71	24.5	3.98	3.39	85.18	3.93	8.62	74	130	90
24.	26	167	52	18.6	3.97	3.26	82.12	3.67	9.29	64	110	60
25.	30	175	78	25.5	4.99	4.19	83.97	3.85	9.85	84	120	70
26.	42	149	56	25.22	2.2	1.84	83.64	2.49	5.37	64	110	70
27.	37	144	46	22.1	2.59	2.29	88.42	2.83	7.43	74	110	70
28.	40	149	47	21.17	2.5	2.01	88.08	2.74	5.67	84	100	60
29.	22	150	51	22.66	3.18	2.78	87.42	3.25	6.54	64	120	80
30.	37	157	62	25.15	2.62	2.22	84.73	3.47	6.5	84	130	80

S.NO	FAMILY H/0	Mean RR	Mean HR	SDNN ms	RMSSD ms	NN50 counts	pNN50 %	VLF ms^2	LF ms^2	HF ms^2	LF/HF	LF nu	HF nu
1.	NO	0.791	76	68.896	49.232	99	32.2	6204	846	32	6.33	86.4	13.6
2.	NO	0.815	74	62.814	58.766	128	49.2	7073	1275	129	1.46	59.3	40.5
3.	NO	1.095	65	90.464	85.744	39	50.6	3359	154	82	2.51	71.6	28.4
4.	NO	1.053	67	151.348	78.352	54	50.5	4279	185	106	2.52	71.6	28.4
5.	NO	0.737	81	78.971	46.336	70	48.6	65	15	55	2.48	71.5	28.8
6.	NO	0.759	79	54.872	36.867	72	19.1	784	272	76	1.37	57.9	42.1
7.	NO	0.654	76	79.417	46.034	62	12.4	18	38	82	8.4	80.8	19.2
8.	NO	0.939	64	57.309	34.036	51	14.2	2434	232	23	2	66.7	33.3
9.	NO	0.766	78	42.549	37.61	28	7.4	1548	442	65	2.47	71.2	28.8
10.	NO	0.793	76	57.569	56.651	138	44.8	1328	274	272	4.46	81.7	18.3
11.	YES	0.716	84	31.918	77.724	24	9.9	87	134	37	1.24	80.2	19.8
12.	NO	0.8	75	38.069	30.7	36	9.4	1727	264	65	3.64	79.1	21.7
13.	NO	0.776	77	33.205	72.446	27	11.8	737	145	145	4.5	60	40
14.	NO	0.758	70	105.8	48.488	33	10.6	43	54	83	5.27	65.5	34.5
15.	NO	0.961	62	62.924	35.144	49	14.9	1603	397	186	1.34	57.3	42.7

S.NO	FAMILY H/0	Mean RR	Mean HR	SDNN ms	RMSSD ms	NN50 counts	pNN50 %	VLF ms^2	LF ms^2	HF ms^2	LF/HF	LF nu	HF nu
16.	NO	0.691	78	33.901	36.099	96	18.7	40	55	165	2.76	72.5	26.5
17.	NO	0.739	81	99.305	33.188	51	11.8	151	69	101	2.61	72.3	27.7
18.	YES	0.686	76	32.977	50.816	28	14.7	145	74	88	2.53	71.7	28.3
19.	NO	0.642	76	96	55.639	33	17.3	49	67	79	2.17	68.5	31.5
20.	NO	0.792	76	30.382	64.071	25	14	2120	300	46	1.64	62.3	37.9
21.	NO	0.801	75	52.589	62.628	155	54.7	7232	1005	22	2.3	70.2	29.8
22.	NO	0.712	84	34.755	43.168	25	21.1	19	12	23	1.81	64.5	35.5
23.	NO	0.85	75	62.221	52.87	89	41.8	6964	925	58	3.09	75.6	24.4
24.	NO	0.936	64	50.294	52.569	148	41.8	4100	593	41	1.00	50.1	50
25.	NO	0.704	85	48.635	30.717	46	11.5	1164	276	69	3.5	77.8	22.2
26.	NO	0.958	63	44.965	59.078	156	49.2	6422	801	23	1.32	56.9	43.1
27.	NO	0.759	75	81.995	35.889	88	18.9	48	38	108	3.88	79.5	20.5
28.	NO	0.718	84	84.212	53.093	45	31.1	112	34	52	2.83	73.9	26.1
29.	NO	1.124	63	47.478	79.301	256	63.7	9958	872	37	10.04	45.5	54.5
30.	NO	0.724	83	85.214	56.162	26	15.9	214	84	227	2.91	73.7	25.3